



(19)

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) EP 1 217 066 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
26.06.2002 Bulletin 2002/26

(51) Int Cl.7: C12N 15/11, C07K 14/705,
A61K 38/17, G01N 33/68

(21) Application number: 00870316.7

(22) Date of filing: 21.12.2000

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(71) Applicant: UNIVERSITEIT GENT
9000 Gent (BE)

(72) Inventor: The designation of the inventor has not
yet been filed

(74) Representative: De Clercq, Ann et al
De Clercq, Brants & Partners cv,
Edgard Gevaertdreef 10a
9830 Sint-Martens-Latem (BE)

Remarks:

The sequence listing, which is published as annex
to the application documents, was filed after the date
of filing. The applicant has declared that it does not
include matter which goes beyond the content of the
application as filed.

(54) Modulation of ATP-binding cassette transporter activity

(57) The invention relates to the field of ATP-Binding
Cassette (ABC) transporter molecules, and to mole-
cules selectively modulating the activity of said ABC
transporters. Herein are provided molecules and com-
pounds which selectively modulate the activity of specific

ABC transporters. The invention also relates to mole-
cules, compounds and compositions for preventing,
treating or alleviating cancer or diseases related to bac-
terial, fungal or protozoal infections.

EP 1 217 066 A1

Description**FIELD OF THE INVENTION**

5 [0001] The invention relates to the field of ATP-Binding Cassette (ABC) transporter molecules and to molecules selectively modulating the activity of said ABC transporters.

BACKGROUND OF THE INVENTION

10 [0002] The ATP-binding cassette (ABC)-transporters constitute one of the largest and most highly conserved protein super families, which are found in large numbers in all organisms (Holland and Blight, 1999). These transmembrane proteins transport a wide range of compounds through biological membranes. The ABC transport proteins can import essential nutrients into cells, such as ions, sugars, amino acids etc... ABC-transporters can further protect cells by exporting a wide range of toxic compounds, signal the presence of infectious agents, and regulate development in
15 microorganisms and mammals (Higgins, 1992). ABC-transporters participate in the regulation of several tissues such as the liver, lungs, retina and the immune system (Holland and Blight, 1999; Higgins, 1992). Consequently, mutations affecting ABC-transporters are associated with a variety of human inherited diseases, including the cystic fibrosis transmembrane conductance regulator (CFTR) linked to cystic fibrosis (Sheppard and Welsh, 1999), and the ABC-A1 transporter linked to Tangier Disease (Rust *et al.*, 1999; Bodzioch *et al.*, 1999; Brooks-Wilson *et al.*, 1999). Disease treatment is also dependent upon the function of ABC-transporters. For example in cancer treatment, expression of
20 the P-glycoprotein or MDR1 (multidrug resistance gene product) in cancer cells, confers multidrug resistance against chemotherapeutic agents and decreases the efficacy of treatment (Borst *et al.*, 1986; Hopfner *et al.*, 1999). The resistance of some bacteria to certain classes of antibiotics can be attributed to the activity of transmembrane ABC transporters (Higgins, 1992).

25 [0003] ABC-transporters consist of at least two basic subunits : an ATPase domain (also named NBD (domain) or (nucleotide binding domain)) which provides the energy required for the transport function, and a domain composed of six membrane-spanning helices, which form a channel and confer substrate specificity. Most ABC-transporters function as oligomers consisting of two ATPase and two transmembrane domains, which are either encoded separately, or tandemly replicated within a single polypeptide (Fig. 1). The transport of compounds across the membrane is accompanied by ATP hydrolysis. The ATPase domain becomes activated by binding of the allocrite and provides energy for transmembrane transport. It is thus obvious that there is strong cooperativity between the TM and ATPase domains of the ABC-transporters and they cannot function independently.

30 [0004] ATPase domains, homologous to those of the ABC-transporters have recently been identified in DNA repair proteins such as in Rad50, where it was found associated to a DNA binding domain (Hopfner *et al.*, 2000). ATP hydrolysis by the ATPase domain of Rad50 provides the energy required for DNA binding and dissociation. In ABC-transporters, the two ATPase domains or NBD's do not function separately but rather show cooperative ATP hydrolysis, allosterically regulated by ligand binding (Higgins, 1992).

35 [0005] The crystal structure recently reported for a dimer of the ATPase domains of the Rad50, protein, shows that conserved motifs, in the ATPase domains form a dimerization interface. This interface holds both the ATP molecules and the two NBD monomers in an optimal conformation for the function of the transporter (Hopfner *et al.*, 2000).

Sequence and structure of the ATPase domains of ABC-transporters.

40 [0006] At the sequence level, ABC-ATPases are well conserved, displaying 30 % or more identity between different ABC-transporters. This identity is concentrated in several motifs, which have been used for the recognition of new ABC-transporters. The following sequence elements are typical for ABC-transporter NBD domains: the P-loop or Walker A motif: GAXXGXGKS/TT, where X can be any residue, which is critical for the binding of the beta-phosphate of the ATP nucleotide; the Walker B motif (consensus : HyHyHyHyDE where Hy is a hydrophobic residue). Upstream of the Walker B motif there is a signature motif, SXG where X is mostly G, which is typical for ATPases in ABC-transporters.
45 Except for the Walker A motif, the functional significance of the other structural motifs was unclear until the crystal structure of several ABC transporters became available.

50 [0007] The crystal structure of HisP from *Salmonella typhimurium* (Hung *et al.*, 1998), showed that the overall shape of the NBD domain is that of an "L", with two arms or lobes (I and II). Lobe I consists primarily of an $\beta/\alpha/\beta$ fold formed by the packing of helix A between two β -sheets consisting of six hydrogen-bonded (3 strands. Lobe II is generated by the packing of three helices against a five-stranded mixed β -sheet. The two lobes are joined into a single folded domain by a central beta-sheet II. The nucleotide binding site formed by the Walker A motif (P loop), is located in Lobe I near the interface of both lobes.

55 [0008] Several studies have shown that the two NBD domains, NBD1 and NBD2, of ABC-transporters function co-

operatively and that inactivation of one catalytic site completely abolishes ATPase activity and transport function (Holland and Blight, 1999; Higgins, 1992). This can be achieved either by mutations in the Walker A or Walker B site, or by vanadate trapping (Holland and Blight, 1999) of ADP in the catalytic sites. An allosteric regulation of the cooperativity between the two NBD domains is probably a mode of "fine" regulation of these transporters.

- 5 [0009] The ABC-transporter family represents a class of proteins with widespread distribution in the human organism sufficing a variety of functions. Moreover, related ABC-transporters are prominent in other eukaryotes and bacteria. A possible way to interfere with the function of these transporters would be to prevent the binding of ATP. Alignment of the nucleotide binding domains of different ABC transporters from mammal and bacterial origin already enabled the identification and localization of the structural elements in the NBD domains of these transporters. Since these elements
10 and especially the P loop are well conserved, problems arise when searching for means of blocking specific ABC-transporters without interfering with the action of other vital members of this protein family. Therefore it is an aim of the present invention to identify molecules and compounds which selectively modulate the activity of ABC transporters.
[0010] It is furthermore an aim of the present invention to provide methods for identifying and inhibiting the dimeric interfaces between the two ATPase domains of ABC-transporters. It is another aim of the invention to provide molecules,
15 compounds and compositions for preventing, treating or alleviating cancer or diseases related to bacterial, fungal and protozoal infections.

SUMMARY OF THE INVENTION

- 20 [0011] Three stretches of sequence are crucial for the heterodimeric NBD1-NBD2 structure of ABC-transporters: the residues corresponding to the signature motif, the Walker B motif and the D loop. The present inventors have identified the D-loop as the third important sequence which is conserved amongst ABC transporters. The D-loop immediately follows the Walker B motif and has been named as such by the inventors because they surprisingly found that the last amino acid (Aspartic acid, D) at the end of the conserved loop is very conserved among known ABC-transporter molecules. From several studies supported by extensive molecular modelling of the nucleotide binding domains of HisP, Rad50 and ABC-A1, the present inventors found that this D-loop is also structurally conserved amongst ABC-transporters and forms a central protein-protein dimerization interface (Figure 2). Contacts between the central residues of the D loop may contribute to the optimal dimer interface configuration. A central residue in the D loop could also be involved in the nucleophile attack on the ATP γ phosphate, through hydrogen bonding of an attacking water molecule.
25 [0012] As described above, the signature motif and Walker A motif, which are part of the dimer interface, belong to the best-conserved elements of the ATPase of ABC-transporters. Until now, the sequence and structure conservation of the D loop had not been described yet for the ABC-transporters. Using the sequence multiple alignment programs, the present inventors identified and analyzed the sequence conservation of these motifs in the ABC-transporters family. Consensus sequences for the D loop in different families of human ABC transporters and in bacterial, protozoal, fungal,
30 and yeast ABC transporters are listed in Tables 1 and 2.

The D-loop as target for inhibition of dimerization of ABC-transporters

- 35 [0013] Assembly of different proteins or of different domains within the same protein is a widespread mechanism used for growth and cellular control (Zutshi *et al.*, 1998). Many enzymes, viral proteins, and receptor-ligand interactions are comprised of oligomeric protein complexes (Jones and Thornton, 1996). Assembly of entire proteins or of protein domains are essential elements in allosteric control (Frieden, 1971), signal transduction, viral assembly and replication (Gibson, 1996). The ubiquitous nature of protein-protein interactions in essential cellular processes provides the possibility of developing novel control mechanisms based on inhibition of active protein assemblies. In the past five years, 40 protein-protein interactions in viral enzymes and receptors were inhibited by peptides and small molecules, which led to the development of new antiviral drugs (Brickner and Chmielewski, 1998).
[0014] In the structure of the NBD1-NBD2 heterodimer, only the D-loop provides both efficiency and selectivity for inhibition or enhancement of dimerization of selected transporters. The D-loop residues ensure protein-protein interactions which are specific for sub-families of transporters, whereas dimerization via the signature and Walker A motif 45 involves ATP binding and hydrolysis, a mechanism common to all transporters in the entire ABC family.

DETAILED DESCRIPTION OF THE INVENTION

- 50 [0015] The present invention relates to a method for selectively modulating the activity of ABC transporters. One of the possible ways to modulate the activity of ABC transporters is by influencing the dimerization of the nucleotide binding domains.
[0016] Therefore, according to a first embodiment the present invention relates to a method for selectively modulating the activity of ABC transporters by influencing the dimerization of the nucleotide binding domains comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids comprising the D loop sequence of an ABC transporter,
 b) a polypeptide consisting of the D loop sequence of an ABC transporter,
 c) a peptide mimetic of any of the polypeptides of a) or b), or,
 d) an antisense peptide of the polypeptides of a) or b).

5

[0017] A list of known human ABC transporter molecules organized by family is provided in Table 1. In Table 2 bacterial, fungal and protozoal ABC transporters are listed. The amino acid sequences of some known examples of ABC transporters are listed in Figure 3.

10

[0018] The human ABC transporters have been organized in subfamilies, trivially named from ABCA to ABCF transporters and recently reviewed by Klein et al. (1999). Some of these transporters are generally known by their common names, as additionally noted in Table 1 and Figure 3. For instance, the multidrug resistance proteins or P-glycoproteins, now belonging to the ABCB transporters, have been long known as MDR proteins or belonging to the MDR/TAP subfamily.

15

[0019] In Table 1 and 2, the amino acid sequences of the D loop (in NBD1 and NBD2) are given for each member of the ABC transporter family listed. The D loop sequences are represented in SEQ ID NOs 1 to 43. In cases where only one nucleotide binding domain is present in the protein, for instance when the ABC transporter consists of at least two monomers or subunits, only one D loop sequence is noted in the table(s).

[0020] The expression "ABC transporter(s)", "ABC transporter protein(s)" and "ABC transporter molecule(s)" as used herein are interchangeable.

20

[0021] As used herein the terms "peptides" and "polypeptides" are interchangeable.

[0022] The term "modulating" relates to increasing, decreasing, inhibiting, abolishing or blocking the activity of selected transporters or groups of transporters within the ABC transporter family. For instance inhibiting the activity results at least in preventing the NBD1-NBD2 hetero-dimerization in such a way that the overall function of the ABC transporter in transporting molecules from one side to the other side of the cellular membrane is affected.

25

[0023] The expression "selectively modulating the activity" means that only the activity of one specific or at most a few very closely related ABC transporter molecules will be modulated in such a way that it influences the normal activity of said molecule. The "selectivity" resides in the amino acid sequence of the D loop of the nucleotide binding domain (s) of each particular ABC transporter molecule.

30

[0024] With the expression "D loop" is meant a sequence of 6 to 8 amino acids (ending with an aspartic acid (D)) which immediately follows the highly conserved Walker B motif in the primary structure of the ABC transporters. In each NBD domain of an ABC transporter, a D loop is present at the dimerization interface between the nucleotide binding domains. Interactions between the two D loops or between residues from one D loop and the ATP molecule bound by the second NBD play a key role in the dimerization of NBD's, and as such in the activity of the ABC transporter.

35

[0025] Therefore, in a more preferred embodiment the invention relates to a method for selectively modulating the activity of ABC transporters by influencing the dimerization of the nucleotide binding domains comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 1 to 43,
 b) a polypeptide consisting of the amino acid sequence as represented in any of SEQ ID NOs 1 to 43 or a functional homologue thereof,
 c) a peptide mimetic of any of the polypeptides of a) or b), or,
 d) an antisense peptide of the polypeptides of a) or b).

40

[0026] The expression "influencing the dimerization" can be used for inhibiting or blocking the formation of dimeric interfaces between the two ATPase domains of an ABC-transporter molecule.

[0027] The expression "functional homologue" relates to the corresponding sequences identifiable in other related ABC transporter molecules or relates to the homologous ABC transporter molecule from other organisms. As can be seen from Tables 1 and 2, some of the human ABC transporters have a bacterial or protozoal homologue with an identical D loop sequence. For instance, the D loop sequence of the human ABC transporter B7, belonging to the group of multidrug resistance proteins, is identical to the Pfmdr2 protein of *Plasmodium falciparum*, also known as a multidrug resistance protein. Therefore, it should also be understood that the person skilled in the art from the information herewith provided will know which D-loop sequence and molecules derived therefrom can be used for modulation of specific ABC transporters.

50

[0028] The expression "peptide mimetic" relates to a molecule that mimics the biological activity of a peptide but is no longer peptidic in chemical structure (Moore, 1996) The term mimetic is sometimes used to describe molecules that are no longer completely peptidic in nature, such as pseudopeptides and peptoids, but a strict definition is a molecule that no longer contains any peptide bonds and has a molecular weight of less than 700 daltons. The production and use of peptide mimetics is known to the one skilled in the art (see for instance Zutshi et al. (1997)).

- [0029] The term "antisense peptide" is reviewed by Blalock (1990) and by Roubos (1990). In this respect, the molecular recognition theory (Blalock, 1990) states that not only the complementary nucleic acid sequences interact but that, in addition, interacting sites in proteins are composed of complementary amino acid sequences (sense-receptor ligand or sense-antisense peptides). Thus, two peptides derived from complementary nucleic acid sequences in the same reading frame will show a total interchange of their hydrophobic and hydrophilic amino acids when the amino terminus of one is aligned with the carboxy terminus of the other. This inverted hydropathic pattern might allow two such peptides to assume complementary conformations responsible for specific interaction.
- [0030] The present inventors found that the D loop is highly conserved in amino acid sequence as well as in structure among all members of ABC transporter family. Nevertheless, said D loop still displays sufficient variability between subfamilies and even between members of a single subfamily to serve as a target for selective interaction with inhibitory peptides or peptide mimetics. In some ABC transporter subfamilies (e.g. ABCB transporters) the sequence of the D loop seems to be conserved in all members of this subfamily for NBD2. In other families, a consensus sequence can be deducted for the D loops (in NBD1 and/or NBD2), as represented in Table 1. Therefore, in some applications it is possible to modulate or block the activity of all members of a specific ABC transporter subfamily using only one polypeptide prototype. Otherwise, in other ABC transporter subfamilies, the activity of specific members can be modulated because sufficient variability in the amino acid sequences of the respective D loops exists. Additionally, in the latter case is it also possible to modulate the activity of all members of said specific ABC transporter subfamily, provided that the consensus D-loop sequence (Tables 1 and 2) is used as a prototype polypeptide.
- [0031] The term "prototype polypeptide" should be interpreted as the consensus sequence for the D-loop (e.g. for the ABCG transporter family, the consensus sequence represented in SEQ ID NO 36) on which all possible variants are patterned (e.g. the amino acid sequences represented in SEQ ID NOs 34 and 35).
- [0032] "Very closely related" ABC transporter molecules for instance are molecules belonging to the same subfamily.
- [0033] Furthermore, it is known that different isoforms exist for particular ABC transporter molecules. The invention thus also relates to possible variants of the D loop between isoforms of the same ABC transporter molecule.
- [0034] It should be understood that the possible function and importance of the D loop has not been recognized until the present invention. Also, not all the sequences of ABC transporters are known so that also the consensus sequences for the NBD domain(s) of the transporter(s) may change. Nevertheless it should be recognized that the present invention relates to a general concept and applications of the D loop, which was recognized for the first time by the present inventors. It should therefore, be understood that the invention also relates to all applications and research tools wherein the existence, and the duality between "conserved" and at the same time "variability within the sequence" of the D-loop is used in any possible way already known in the art.
- [0035] Furthermore, it should be understood that according to the present invention, molecules comprising the D loop sequences itself can be used or the D loop sequences can be used as a target for modulation or blocking.
- [0036] In a preferred embodiment, the invention thus relates to a method for selectively decreasing (or increasing) the activity of an ABC transporter.
- [0037] One way of modulating the activity of an ABC transporter is by blocking (or inhibiting) one of the D loops in the dimerization event for instance by a molecule comprising the corresponding amino acid sequence of the second D loop.
- [0038] In several diseases associated with the functionality of ABC transporters, inhibition or blocking of the activity of ABC transporters can be beneficial for therapy. Some examples of such ABC transporters are given in bold in Table 1.
- [0039] According to the invention, the activity of specific members of the ABC transporter family or groups (e.g. subfamilies) of ABC transporters can be modulated using specific prototype polypeptides as a target.
- [0040] Therefore according to a preferred embodiment, the invention relates to a method for selectively modulating, preferably inhibiting or blocking, the activity of an ABC transporter, wherein said ABC transporter belongs to the group of multidrug transporter/P-glycoproteins comprising the use of:
- a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NO 1 to 3, more preferably SEQ ID NO 1 and SEQ ID NO 2,
 - a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NO 1 to 3, or a functional homologue thereof,
 - a peptide mimetic of any of the polypeptides of a) or b), or,
 - an antisense peptide of the polypeptide of a) or b).
- [0041] Furthermore, the invention also relates to a method for selectively modulating, preferably inhibiting or blocking, the activity of an ABC transporter wherein said ABC transporter belongs to the group of the multidrug resistance associated proteins comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 4 to 15, more preferably SEQ ID NOs 4, 5, 7, 8, 9, 10, 11, 12, 13, 14 or 15,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 4 to 15, more preferably SEQ ID NOs 4, 5, 7, 8, 9, 10, 11, 12, 13, 14 or 15, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the polypeptide of a) or b).

[0042] The ABC transporter molecules belonging to the group of the multidrug transporter/P-glycoproteins and/or multidrug resistance associated proteins are very important in diseases such as cancer.

[0043] The multidrug resistance protein or P-glycoprotein (MDR1 or Pgp1) was the first human ABC protein cloned and is still one of the most intensively studied proteins of the family of the ABCB transporters. This special attention was attracted by the fact that multidrug resistance of cancer cells was found to be caused by this protein.

[0044] Other important candidate ABC transporters belonging to this group are the TAP1 and TAP2 transporters which are associated with antigen processing which activity needs to be suppressed upon transplantation of organs. For the moment, blocking of the activity of said transporters needs the administration of high doses of drugs such as cyclosporine. Reduction in the use of this cyclosporine and avoiding the rejection of the transplant by inhibition of the TAP transporter would increase the success of the transplant.

[0045] Additionally, also the human multidrug resistance associated protein (belonging to the MRP/CFTR or ABCC transporters) confers multidrug resistant phenotype to tumor cells. The majority of non-P-glycoprotein mediated multidrug resistance is due to the over-expression of hMRP1. HMRP1 transports both hydrophobic anticancer agents and anionic (e.g. glutathione) drug conjugates. Its physiological functioning may provide a wide range of cellular xenobiotic resistance. Therefore ABC transporters belonging to this family are especially envisaged in several applications of the present invention.

[0046] Alternatively, the modulation of the activity of an ABC transporter can also result in an improvement of the binding or dimerization of the nucleotide binding domains. Said improvement can be the result of an increase in length of the binding-time period or can be the result of an increase in frequency of dimerization events per time period between the nucleotide binding domains. A positive effect on the dimerization can for instance be achieved by the activity of small peptides or peptide mimetics which directly or indirectly interact with the D loop in a structural (conformational) sense or in an interaction between or with the amino acids constituting the D-loop motif.

[0047] One example of an ABC transporter which is envisaged to benefit from enhancement of activity or of increasing the dimerization event is for instance the CFTR transporter (cystic fibrosis transmembrane conductance regulator). The CFTR transporter is involved with the transport of chloride ions through the membrane. Increasing the activity of said transporter would be beneficial for the treatment of cystic fibrosis patients in which said transporter is defective.

[0048] Also the activity of other ABC transporters can be modulated in a way that increasing the activity is beneficial for therapy. Some examples of such ABC transporters are underlined in Table 1.

[0049] According to a further preferred embodiment the invention relates to a method for selectively modulating, preferably enhancing, the activity of an ABC transporter wherein said ABC transporter is the cystic fibrosis transmembrane conductance regulator (CFTR) comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 11 or 12,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 11 or 12, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

(claims 24-28) Therefore the present invention also relates to the use of a (poly)peptide, antisense peptide or peptide mimetic as defined above or a compound obtainable by one of the compound screening methods described further for treatment of cancer, optionally in combination with chemotherapy. Said (poly)peptides, antisense peptide, peptide mimetic or compound can also be used for treating resistance to drugs in mammals. Said (poly)peptide, antisense peptide, peptide mimetic or compound can also be used for the preparation of a medicine for treating cancer or for preventing, treating or alleviating diseases associated with drug resistance in a mammal.

[0050] ABC transporters are not only important in humans or higher eukaryotes but also bacterial, fungal and protozoal ABC transporters are known wherein a D loop can be recognized as an important structural feature for dimerization and/or functionality and/or activity of said transporter.

[0051] Therefore according to yet another preferred embodiment, the invention relates to a method for selectively modulating the activity of an ABC transporter wherein said ABC transporter is a bacterial transporter comprising the

use of:

a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50
amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 27, 37 to 39,

- 5 b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 27, 37 to 39, or a
functional homologue thereof,
c) a peptide mimetic of any of the polypeptides of a) or b), or,
d) an antisense peptide of the peptide of a) or b).

10 [0052] According to yet another preferred embodiment, the invention relates to a method for selectively modulating
the activity of an ABC transporter wherein said ABC transporter is a fungal ABC transporter, comprising the use of:

a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50
amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 40 to 42,

- 15 b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 40 to 42, or a functional
homologue thereof,
c) a peptide mimetic of any of the polypeptides of a) or b), or,
d) an antisense peptide of the peptide of a) or b).

20 [0053] According to yet another preferred embodiment, the invention relates to a method for selectively modulating
the activity of an ABC transporter wherein said ABC transporter is a protozoal ABC transporter, comprising the use of:

a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50
amino acids, comprising the amino acid sequence represented in any of SEQ ID NO 2, 8 or 43,

- 25 b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 2, 8 or 43, or a functional
homologue thereof,
c) a peptide mimetic of any of the polypeptides of a) or b), or,
d) an antisense peptide of the peptide of a) or b).

30 [0054] Preferably, said bacterial, fungal or protozoal ABC transporter(s) is involved in bacterial, fungal or protozoal
infection of a mammal.

[0055] According to a further preferred embodiment, said bacterial, fungal or protozoal ABC transporter is involved
in the induction of resistance to antibiotics or other drugs in mammals.

[0056] The activity of bacterial, fungal or protozoal ABC transporters can be explained in a way that they transport
35 antibiotics (or certain classes of antibiotics, or other drugs) which are administered to a human or other mammal in
need thereof, to the outside of the bacterial or fungal or protozoal cell wall so that said antibiotics can not exert their
anti-bacterial or anti-fungal or anti-protozoal action. Therefore, the (poly)peptides or antisense peptides, or peptide
mimetics or compounds that specifically block the ABC transporters in bacteria, fungi and protozoa could potentially
40 be used for the treatment of infections caused by these pathogens. For instance blocking the D loops in the ABC
transporters of said pathogens might result in a specific treatment method for bacterial, fungal or protozoal infections.
The resulting inhibition of ABC transporter function in these pathogens will cause the death of said pathogen and will
be beneficial to the patients. As such these (poly)peptides antisense peptides, peptide mimetics or compounds can
be considered as an alternative for antibiotics, antifungicide or anti-protozoal treatment for instance in cases in which
a number of organisms have developed already a drug resistance.

45 [0057] Also co-administration of (poly)peptides or antisense peptides, or peptide mimetic which inhibit or block the
activity of bacterial ABC transporters which are involved in such processes or compounds obtainable by one of the
compound screening methods described further together with the antibiotic (or drug) would be beneficial to the anti-
bacterial action of said antibiotic (or drug).

[0058] Therefore, according to another embodiment the invention also relates to the use of a molecule selected from :

- 50 a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50
amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 2, 8, 29 and 37 to 43,
b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 2, 8, 29 and 37 to 43,
or a functional homologue thereof,
55 c) a peptide mimetic of any of the polypeptides of a) or b), or,
d) an antisense peptide of the peptide of a) or b),

as a anti-bacterial or ant-fungal or anti-protozoal agent.

[0059] It should be noted that SEQ ID NOs 2, 8, and 29 have a homologue in human ABC transporters. However the person skilled in the art perfectly knows which molecules or sequences represented by their SEQ ID NOs to choose when the activity of only bacterial and/or fungal and/or protozoal ABC transporters needs to be modulated. For instance in case an anti-bacterial agent is used, molecules based on SEQ ID NO 43 will be used and not for instance based on SEQ ID NO 2 or 8.

[0060] The recognition of the D-loop as a tool for selectively modulating the activity of ABC transporters can be further exploited in therapy for instance for treatment or for preparation of medicaments.

[0061] Therefore the invention also relates to a method for preventing, treating or alleviating diseases associated with the functionality of a human ABC-transporter comprising the use of:

- 10 a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 1 to 36,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 1 to 36, or a functional homologue thereof,
- 15 c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0062] Alternatively the invention also relates to a method for the preparation of a medicament for the prevention, treatment or alleviation of diseases associated with the functionality of a human ABC-transporter comprising the use of:

- 20 a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 1 to 36,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 1 to 36, or a functional homologue thereof,
- 25 c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0063] The invention furthermore relates to a method for preventing, treating or alleviating diseases related with bacterial infections comprising the use of:

- 30 a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39, or a functional homologue thereof,
- 35 c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0064] Alternatively the invention also relates to a method for the preparation of a medicament for the prevention, treatment or alleviation of diseases associated with bacterial infections comprising the use of:

- 40 a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39, or a functional homologue thereof,
- 45 c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0065] The invention furthermore relates to a method for preventing, treating or alleviating diseases related with fungal infections comprising the use of:

- 50 a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 40 to 42,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 40 to 42, or a functional homologue thereof,
- 55 c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0066] Alternatively the invention also relates to a method for the preparation of a medicament for the prevention,

treatment or alleviation of diseases associated with fungal infections comprising the use of:

a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 40 to 42,

5 b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 40 to 42, or a functional homologue thereof,

c) a peptide mimetic of any of the polypeptides of a) or b), or,

d) an antisense peptide of the peptide of a) or b).

10 [0067] The invention furthermore relates to a method for preventing, treating or alleviating diseases related with protozoal infections comprising the use of:

a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 2, 8, or 43,

15 b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 2, 8 or 43, or a functional homologue thereof,

c) a peptide mimetic of any of the polypeptides of a) or b), or,

d) an antisense peptide of the peptide of a) or b).

20 [0068] Alternatively the invention also relates to a method for the preparation of a medicament for the prevention, treatment or alleviation of diseases associated with protozoal infections comprising the use of:

a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 2, 8, or 43,

25 b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 2, 8 or 43, or a functional homologue thereof,

c) a peptide mimetic of any of the polypeptides of a) or b), or,

d) an antisense peptide of the peptide of a) or b).

30 [0069] The present invention also relates to the use of any of the molecules as defined above or a compound obtainable by any of the compound screening methods described further for preventing, treating or alleviating diseases associated with bacterial, fungal or protozoal infections or for the preparation of a medicament for preventing, treating or alleviating diseases associated with bacterial, fungal or protozoal infections. Furthermore, these molecules or compounds may be used for treating resistance to antibiotics in a mammal or for preparing a medicament for treating resistance to antibiotics or other drugs in a mammal.

35 [0070] According to another embodiment, the present invention provides methods of identifying compounds which selectively modulate, inhibit, activate or interfere with the properties of ABC transporters. Compounds may carry agonistic or antagonistic properties. The compounds to be screened may be of extracellular, intracellular, biologic or chemical origin.

40 [0071] Such a screening method may comprise the following steps (a) contacting a compound to be tested with at least one of the polypeptide as defined above under any of a) to d) or with a polypeptide corresponding to the D loop or a nucleotide binding domain of an ABC transporter, (b) detecting a diminution or inhibition of the activity of said ABC transporter, and, (c) identifying said compound.

45 [0072] Alternatively, in step (b) of the above mentioned method, the effectiveness of said compound can also be investigated by measurement of the ATPase activity in case the compound is contacted with a functional ATPase domain (nucleotide binding domain). Methods to measure ATPase activity are known in the art but are also described further in the examples section.

50 [0073] The polypeptides according to the invention employed in such a method may be for example in solution or coated on suspended beads. Alternatively, these can be affixed to a solid support, borne on a cell or phage surface or located intracellularly.

[0074] When polypeptide fragments are coated on solid supports, they can be tested for their binding affinity for large numbers of compounds. These can be used in different kinds of high throughput screenings in order to identify compounds having suitable binding affinity to the polypeptides according to the invention. Platform technologies or technologies based on SPR (surface plasmon resonance) can be applied.

55 [0075] The invention also relates to methods for identifying compounds which selectively bind to or selectively modulate the properties of ABC transporters, which method comprises:

a) providing a yeast two-hybrid system wherein the nucleotide binding domains NBD1 and NBD2 of an ABC trans-

porter are expressed, or,
 b) providing a mammalian expression system wherein the nucleotide binding domains NBD1 and NBD2 of an ABC transporter are expressed, or,
 c) providing a bacterial expression system wherein the nucleotide binding domains NBD1 and NBD2 of an ABC transporter are expressed (and/) or secreted, and,
 5 d) interacting said compound with the complex formed by the expressed polypeptides as defined in any of a) to c),
 e) inferring from the interaction between said compound and one of the nucleotide binding domains a modulation
 of the properties of said ABC transporter, and,
 f) identifying said compound.

10 [0076] Compounds found using this approach and modulating the activity of a selected ABC transporter may additionally be tested on their efficiency to modulate other ABC transporter in order to avoid undesired cross-activity of said compounds on non selected ABC transporters.

15 [0077] Alternatively additional tests can be performed to test the influence of the compound onto protein stability, post-translational modification, precursor processing and protein translocation. All these aspects influence the concentration and/or activity of corresponding proteins and consequently influence the effect of these onto the metabolism of the cell. Also here, medium or low throughput systems can be used to confirm results obtained by the high throughput assays.

20 [0078] Compounds obtainable by one of the methods described above or the use of said compounds as a medicament also form part of the invention.

[0079] The invention also relates to an isolated nucleic acid encoding at least one of the polypeptides defined above in a) to d) comprising an ABC transporter D loop represented in any of SEQ ID NOs 1 to 43.

[0080] The invention further relates to a polypeptide encodable by an isolated nucleic acid as defined above.

25 [0081] The invention also relates to a composition, preferably a pharmaceutical composition, comprising at least one polypeptides of the invention and to the use of said polypeptide or of the composition comprising said polypeptide as a medicament.

[0082] The invention also relates to a cellular host for use in a method described above, said cellular host transformed with a nucleic acid encoding at least one nucleotide binding domain of an ABC transporter protein or a nucleic acid comprising a nucleic acid as described above, said nucleic acid in an expressible format.

30 [0083] The cellular hosts used in the invention can be from bacterial, fungal, vegetal or mammalian origin. There are numerous vectors, expression systems and methods known in the art to allow the skilled in the art for transforming, transfecting or infecting the desired host cell with the desired nucleic acid in order to obtain desired expression of any of the polypeptides of the invention.

35 [0084] The invention, now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention and are not intended to limit the invention. All of the references mentioned herein are incorporated by reference.

BRIEF DESCRIPTION OF TABLES AND FIGURES

40 [0085]

Figure 1. Schematic representation of the ABC transporters.

45 Figure 2. Schematic presentation of positioning of the ATP-binding site and the dimerization-interface in the ABC transporter molecule.

50 Figure 3. Amino acid sequences of human, bacterial, protozoal and fungal transporters: examples. The underlined sequences refer to the D loops in these sequences. The names of the sequences given after each ">" refer to the names given in Tables 1 and 3.

55 Table 1. Sequences of the D loops in different human ABC transporters, and derived consensus sequence for each family. Marked in ***bold** are the candidate transporters for inhibition of activity. Marked underlined are the candidate transporters for increase of activity.

Table 2: Sequences of the D loops in different ABC transporters from bacteria fungi and protozoa. All transporters are candidate transporters for inhibition.

TABLE 1 : D loops in human ABC transporter families.

5

ABCA TRANSPORTERS

10

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
<u>A1</u>	ABC1	PTAGVD PTTGMD	SEQ ID NO 16 SEQ ID NO 17
A2	ABC2	PTAGVD PTTGMD	
A3	ABC-C	PTSGMD PSTGMD	SEQ ID NO 18 SEQ ID NO 19
<u>A4</u>	ABC-R	PTSGVD PTTGMD	SEQ ID NO 20
A7	ABCX	PTAGVD PTTGMD	
A8	ACGA8	PTAGLD PSTGMD	SEQ ID NO 21

15

20

25

CONSENSUS

NBD1 P T A G (V/L) D (SEQ ID NO 22) or P T S G (M/V) D (SEQ ID NO 23)
 NBD2 P (T/S) T G M D (SEQ ID NO 24)

30

ABCB TRANSPORTERS -(MDR/TAP)

35

40

45

50

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
*B1	MDR1 or P GLYCOPROT	ATSA LD ATSA LD	SEQ ID NO 1
B2	TAP1	ATSA LD	
B3	TAP2	ATSA LD	
*B4	MDR2/3	ATSA LD ATSA LD	
B6		ATSA LD	
B7		ATSS LD	SEQ ID NO 2
B8		ATSA LD	
B9		ATSA LD	
B10		ATSA LD	
*B11	SPGP	ATSA LD ATSA LD	

55

CONSENSUS :

NBD1 A T S (A/S) L D (SEQ ID NO 3)
 NBD2 A T S A L D

TABLE 1 - Continued

5

ABCC TRANSPORTERS (MRP/SUR/CFTR)

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
*C1	MRP1 (Multidrug resistance associated protein)	PLSAVD ATAAVD	SEQ ID NO 4 SEQ ID NO 5
C2	MRP2	PLSAVD ATAAVD	
C3	MRP3	PLSAVD ATAAID	
*C4	MRP4	PLSAVD ATANVD	SEQ ID NO 6
*C5	MRP5	PLSALD ATAAMD	SEQ ID NO 8 SEQ ID NO 9
*C6	MRP6	PLAALD ATAAVD	SEQ ID NO 10
C7	CFTR	PFGYLD PSAHLD	SEQ ID NO 11 SEQ ID NO 12
*C8	SUR1 (Sulfonurea receptor)	PFSALD ATASID	SEQ ID NO 13 SEQ ID NO 14
*C9	SUR2	PFSALD ATASID	
C10		PLAAVD ATASVD	SEQ ID NO 15

35

ABCD TRANSPORTERS

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
D1	ALDP	CTSAVSID	SEQ ID NO 25
D2	ALDR	CTSAVSID	
D3	PXMP1	CTSAVSVD	SEQ ID NO 26
D4	PXMP1L	ATSALTEE	SEQ ID NO 27

45

50

55

TABLE 1 - Continued**ABCE TRANSPORTER**

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
E1	RNASELI	PSAYLD	SEQ ID NO 28

ABCF TRANSPORTER

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
F1	MDR	PTNHLD PTNNLD	SEQ ID NO 29 SEQ ID NO 30
F2		PTNHLD PTNHLD	
F3		PTNMULD PTNHLD	SEQ ID NO 31

CONSENSUS

NBD1 P T N (H/M) L D (SEQ ID NO 32)
 NBD2 P T N (N/H) L D (SEQ ID NO 33)

ABCG TRANSPORTERS

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
G1	ABC8White	PTSGLD	SEQ ID NO 34
*G2	BCRP1	PTTGLD	SEQ ID NO 35
<u>G5</u>		PTTGLD	
<u>G8</u>		PTSGLD	

CONSENSUS P T (T/S) G L D (SEQ ID NO 36)

5
10
15
20
25
30
35
40
45
50
55

TABLE 2 : D LOOPS IN BACTERIAL, FUNGAL AND PROTOZOAL ABC TRANSPORTERS

BACTERIA

BACTERIA			
PROTEIN	SEQUENCE	FUNCTION	SPECIES
LmrA	ATASLD	Lincosycin resistance	<i>Streptomyces lincolnensis</i>
DraA	ADQLAD	daurorubicin resistance	<i>Lactococcus lactis</i>
OleB	PTNHLD	oleandomycin resistance	<i>Streptomyces paucetus</i>
	PTNHLIS		<i>Streptomyces coelicolor</i>
			SEQ ID NO 39

FUNGI

FUNGI			
PROTEIN	SEQUENCE	SPECIES	SEQ ID NO
Bfr1	STRGLD	<i>Schizosaccharomyces pombe</i>	SEQ ID NO 40
	PTSGLD		SEQ ID NO 41
Cdr1	ATRGLD	<i>Candida albicans</i>	SEQ ID NO 42
	PTSGLD		
Cdr2	ATRGLD	<i>Candida albicans</i>	
	PTSGLD		
Pdr5p	ATRGLD	<i>Saccharomyces cerevisiae</i>	
	PTSGLD		
Snq2p	ATRGLD	<i>Saccharomyces cerevisiae</i>	
	PTSGLD		

PROTOZOA

PROTOZOA			
PROTEIN	SEQUENCE	FUNCTION	SPECIES
Pfmdr2	ATSSLD	Multidrug resistance protein 2	<i>Plasmodium falciparum</i>
MDR-PLAFS	ATSSLD	chloroquine, me洛quine	<i>Plasmodium falciparum</i>
	ATSSLD	halofantine resistance	Malaria
DVLNS ?	PLSALD	methotrexate resistance	<i>Leishmania tarentolae</i>
	ATANID		SEQ ID NO 43

EXAMPLES**Example 1****5 1. Molecular modeling of the ATP binding cassette (ABC) domain.**

[0086] The ABC-1 transporter contains two different nucleotide binding domains (NBD1 and NBD2), involved in the hydrolysis of ATP. The first structure of a nucleotide binding domain of an ABC transporter that has been determined by crystallization and X-ray diffraction analysis is the ATP binding cassette HisP of the *Salmonella typhimurium* histidine permease. There is significant sequence homology between HisP and both nucleotide binding domains of ABCA1, and the major structure elements of HisP are conserved. The two nucleotide binding domains (NBD) of ABCA1 can therefore be modeled, based on the coordinates of the crystal structure of HisP.

[0087] The structure of the ATPase domain of the Rad50 protein, determined by crystallisation and X-ray diffraction is very similar to the HisP structure. In the presence of a non-hydrolyzable ATP analogue, the Rad50 ATPase crystallised as a dimer. This dimeric structure forms a reliable template to model dimerization of two HisP monomers and to model the putative dimeric configuration of NBD1 and NBD2 of ABCA1 and of other related ABC transporters. From these models, the actual dimer interface is studied in closer detail and mutations impairing dimerization of the nucleotide binding domains are proposed.

20 2. Homology modeling

[0088] Sequence homology and alignments between the NBD domains of different human and bacterial ABC transporters were analyzed using BLAST, CLUSTALX and DIALIGN. Secondary structure prediction were carried out using the PHD, JPRED softwares. 3D homology calculations and model building were performed using MSI Insight 2000 software on a Silicon Graphics 02 computer, combined with SCWRL. Models are checked using Procheck, Prosa II, WHATIF and 3D-profiles.

[0089] The built models for the two ABCA1 ATP nucleotide binding domains allow identification and characterization of the ATP binding site and dimerization site, and the design of ABCA1 mutants that lose either ATP binding, or ATPase activity or without significant structure perturbations. The models also help identify residues involved in protein-protein interactions between NBD1 and NBD2 of ABCA1.

Example 2**1. Cloning of the nucleotide binding domains and transformation of *E. coli*.**

[0090] The ABCA1 cDNA is cloned in the pcDNA3.1 plasmid under control of the T7 promotor. Because no unique restriction sites are present close to the boundaries of the NBD domains the individual nucleotide binding domains are generated by direct PCR of these regions (Taq polymerase). These PCR products are introduced in the pTrcHis TOPO plasmid (Invitrogen) that introduces directly a 6X His tail at the N-terminus and is under control of a Trc promotor. After purification, the His tag can be removed by treatment with enterokinase. Point mutations in these domains are introduced by the Quickchange mutagenesis kit (Stratagene).

[0091] Transformation of TOP10 Oneshot competent *E.coli* is performed by 'heat-shock' at 42°C during 30 seconds. The transformed *E.coli* are grown overnight at 37°C in Luria-Bertani (LB) medium. Plasmid DNA is isolated using the MiniPrep kit (Invitrogen) and checked by sequencing.

45 2. Expression and purification of the nucleotide binding domains

[0092] The optimal conditions for growth and expression are determined using standard procedures. Once the optimal conditions for expression are determined, a larger scale culture is prepared.

[0093] The expressed NBD proteins are isolated from the *E.coli* after lysis of the bacteria by sonication. Nucleic acids are precipitated with streptomycine sulphate (10%) and removed by centrifugation. The supernatant containing the NBD-His proteins is purified by affinity chromatography using a Ni²⁺-agarose matrix (ProBond). The presence of the NBD protein in the eluate is verified by SDS-PAGE and Coomassie staining. The N-terminal 6xHis tag is removed by treatment with enterokinase Max.

Example 3: ATP binding and hydrolysis after incubation with the NBD's.**1. ATP binding using a fluorescent labeled ATP-analogue: 2'-O-(2,4,6-trinitrophenyl) adenosine 5'-trifosfaat (TNP-ATP).**

5 [0094] Unbound TNP nucleotides (Molecular Probes) dissolved in water display no fluorescence emission but become fluorescent once bound to nucleotide binding proteins such as ATPases. 150 µg/ml NBD1 are incubated at 25°C with 2µM TNP-ATP, 0,8 mM EDTA in a 40 mM Tris-HCl buffer (pH 7,4). Fluorescence emission is measured on an Aminco Bowman fluorescence spectrophotometer (excitation wavelength 405 nm, emission 546 nm). The concentration of the TNP-ATP is determined spectrophotometrically at 408 nm using an extinction coefficient of 2,64 x 10⁴ M⁻¹cm⁻¹.

2. ATP hydrolysis measured using radiolabeled ATP.

10 15 [0095] ATP-ase activity is measured as described by Gradia et al. (1997). The NBD proteins (\pm 100 nM) are incubated in 40 mM HEPES (pH 7,8), 75 mM NaCl, 10 mM MgCl₂, 1,75 mM DTT, 0,075 mM EDTA, 15% glycerol, 75 µg/ml acetylated BSA (Promega) and 500 mM ATP supplemented with 1 µCi γ -³²P-ATP. This mixture is incubated during 30 min at 37°C and stopped by adding an excess 10% activated charcoal dissolved in 1 mM EDTA. After removal of the charcoal by centrifugation the ³²P-orthophosphate is measured by liquid scintillation counting.

20 25 3. ATP hydrolysis measured by following the amount of inorganic phosphate formed using a colorimetric assay.

30 [0096] The EnzChek phosphate assay kit (Molecular Probes) permits the measurement of ATPase activity measurements. During the enzymatic reaction the substrate MESG (2-amino-6-mercaptopurineribonucleoside absorbance 330 nm) is converted, in the presence of inorganic phosphate and purine nucleoside phosphorylase (PNP), to ribose-1-phosphate and 2-amino-6-mercaptopurine which absorbs at 355 nm. The change in the absorption maximum of the MESG and the mercaptopurine allows quantification of the inorganic phosphate consumed in the reaction mixture. The NBD proteins are incubated in 50 mM HEPES (pH 7,3) containing 150 mM KCl, 10 mM MgCl₂, 1 mM DTT and 400 µM ATP. The reaction mixture is then mixed with the substrates and enzymes contained in the kit according to the instructions of the manufacturer.

Example 4: Interaction between NBD1 and NBD2**35 1. Gel-filtration**

40 [0097] 50 µg NBD1 and 50µg NBD2 in 50 mM Tris pH 7,4 buffer containing 1mM EDTA, 10 mM MgCl₂ are incubated in the presence or absence of 5mM ATP. This mixture is analyzed on a Superdex 200 column (Pharmacia) in an FPLC system (same buffer). The eluted proteins are followed at 280 nm and the elution volume is used for the calculation of the molecular weight, using a calibration curve with protein standards.

2. Dynamic lightscattering to determine the size of the dimer-monomer

45 [0098] These measurements are performed on a DLS-700 photometer (Otsuka). Samples (NBD1 or NBD 2 only or NBD1/NBD2 mixtures) are prepared at a concentration of \pm 1 mg/ml in a 0.1 M Tris-HCl (pH 7.5) containing 200 mM NaCl and 10 mM MgCl₂ at 22°C. ATP at concentrations up to 10 mM can be added to the mixture to promote dimerization. Scattering intensity is recorded for 5-10 min.

3. Native gradient polyacrylamide gelectroforese.

50 [0099] 4-20% Tris-HCl Ready gels (Biorad) are run in 90 mM Tris-HCl, 2 mM EDTA, 30 mM NaN₃ en 80 mM boric acid. 15 µg NBD protein (either NBD1, NBD2 or the mixture) are incubated with 0,2 µM ATP. After equilibration of the samples they are run on the gel for 1 hour at 70V, and then overnight (with cooling) at 120 V. The gels are stained with Coomassie Brilliant Blue and destained in 40% methanol/10% acetic acid

55 4. Solid phase assay for evaluating of the binding of NBD1 and NBD2

[0100] The NBD1 protein is coated at the surface of polystyrene microtiterplates and the excess protein is washed

(PBS (pH 7.5- Tween 20 0.1%) and remaining binding sites on the plate are blocked with casein (0.1% in PBS pH 7.5). The NBD2 protein is added in increasing amounts to the coated protein in the presence or absence of ATP in a PBS-0.1% casein buffer. Bound NBD2 (containing the N-terminal His tag) is detected using an anti-His monoclonal antibody () followed by incubation with an anti-mouse IgG peroxidase labeled antibody. Alternatively NBD2 directly labelled with peroxidase or alkaline phosphatase can be used for detection. The amount of bound enzyme is revealed using chromogenic or fluorometric substrates. This type of assay can be adapted for evaluation in plasmon resonance technique (BIACORE system (Amersham)), where either NBD1 or NBD2 is adsorbed on the surface.

5. Inhibition of dimerization using competitor peptides or peptides or small compounds blocking the D-loop

10 [0101] The assays mentioned above are performed in the presence of synthetic peptides corresponding to the D-loop (competition) or in the presence of peptides or small compounds that sterically block access to the D-loop (cf. modeling). Peptides are prepared using standard protocols and are added to the incubation mixtures at varying concentrations.

15 6. Evaluation of mutant NBD proteins

20 [0102] As described in the modeling section mutations in the NBD proteins will be proposed. Special emphasis will be given to the mutations aimed at influencing the dimer interface properties of these proteins. The ATPase activity and dimerization properties of the mutant NBDs will be tested as described above.

REFERENCES

[0103]

- 25 Bodzioch M, Orso E, Klucken J, Langmann T, Bottcher A, Diederich W, Drobnik W, Barlage S, Buchler C, Porsch-Ozcurumez M, Kaminski WE, Hahmann HW, Oette K, Rothe G, Aslanidis C, Lackner KJ, Schmitz G: The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease. Nat.Genet. 22:347,1999.**
- 30 Borst P, Zelcer N, van Helvoort A: ABC transporters in lipid transport. Biochim.Biophys.Acta 2000.Jun.26.;1486.(1.):128-44. 1486:128.**
- 35 Blalock, JE: Complementarity of peptides specified by 'sense' and 'antisense' strands of DNA. Trends Biotechnol. 8(6): 140-144, 1990.**
- 40 Brickner M, Chmielewski J: Inhibiting the dimeric restriction endonuclease EcoRI using interfacial helical peptides. Chem.Biol. 5:339, 1998.**
- 45 Brooks-Wilson A, Marcil M, Cleo SM, Zhang LH, Roomp K, van Dam M, Yu L, Brewer C, Collins JA, Molhuizen HO, Loubsen O, Ouellette BF, Fichter K, Ashbourne-Excoffon KJ, Sensen CW, Scherer S, Mott S, Denis M, Martindale D, Frohlich J, Morgan K, Koop B, Pinstone S, Kastelein JJ, Hayden MR: Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency Nat.Genet. 22:336, 1999.**
- Frieden C: Protein-protein interaction and enzymatic activity. Annu.Rev.Biochem. 40:653, 1971.**
- Gibson W: Structure and assembly of the virion. Intervirology 39:389, 1996.**
- Gradia, S., Acharya, S., Fishel, R. The human mismatch recognition complex hMSH2-hMSH6 functions as a novel molecular switch. Cell, 91: 995,1997.**
- Holland IB, Blight MA: ABC-ATPases, adaptable energy generators fuelling transmembrane movement of a variety of molecules in organisms from bacteria to humans. J.Mol.Biol. 293:381, 1999.**
- Higgins CF: ABC transporters: from microorganisms to man. Annu.Rev.Cell Biol. 8:67, 1992.**
- Hipfner DR, Deeley RG, Cole SP: Structural, mechanistic and clinical aspects of MRP1. Biochim.Biophys.Acta 1461:359, 1999.**

EP 1 217 066 A1

Hopfner KP, Karcher A, Shin DS, Craig L, Arthur LM, Carney JP, Tainer JA: Structural biology of Rad50 ATPase: ATP-driven conformational control in DNA double-strand break repair and the ABC-ATPase superfamily. *Cell* 2000.Jun.23.;101.(7.):789.-800. 101:789.

5 Hung LW, Wang IX, Nikaido K, Liu PQ, Ames GF, Kim SH: Crystal structure of the ATP-binding subunit of an ABC transporter. *Nature* 396:703, 1998.

Jones S, Thornton JM: Principles of protein-protein interactions. *Proc.Natl.Acad.Sci.U.S.A.* 93:13, 1996.

10 Klein I, Sarkadi B, Varad A. An inventory of human ABC proteins. *Biochim Biophys Acta* 1461(2): 237-262, 1999.

Roubos E. Sense-antisense complementarity of hormone-receptor interaction sites. *Trends Biotechnol* 8(10): 279-281, 1990.

15 Rust S, Rosier M, Funke H, Real J, Amoura Z, Piette JC, Deleuze JF, Brewer HB, Duverger N, Denefle P, Assmann G: Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1 *Nat.Genet.* 22:352, 1999

Sheppard DN, Welsh MJ: Structure and function of the CFTR chloride channel. *Physiol.Rev.* 79:S23, 1999

20 Zielenski J, Tsui LC: Cystic fibrosis: genotypic and phenotypic variations. *Annu.Rev.Genet.* 29:777, 1995

Zutshi R, Franciskovich J, Shultz M, Schweitzer B, Bishop P, Wilson M, Chmielewski J. Targeting the dimerization interface of HIV-1 protease: inhibition with Cross-linked Interfacial peptides. *J AM Chem Soc*, 119: 4841-4845, 1997

25 Zutshi R, Brickner M, Chmielewski J: Inhibiting the assembly of protein-protein interfaces. *Curr.Opin.Chem.Biol.* 2:62, 1998

30

35

40

45

50

55

SEQUENCE LISTING

<110> UNIVERSITEIT GENT

5

<120> Modulation of ATP-binding cassette transporter activity

<130> UG-013-EP

10

<140> EP 00870316.7

<141> 2000-12-21

15

<160> 92

<170> PatentIn Ver. 2.1

<210> 1

20

<211> 6

<212> PRT

<213> Homo sapiens

25

<400> 1

Ala Thr Ser Ala Leu Asp

1 5

30

<210> 2

<211> 6

<212> PRT

35

<213> Homo sapiens

<400> 2

Ala Thr Ser Ser Leu Asp

1 5

40

<210> 3

45

<211> 6

<212> PRT

<213> Homo sapiens

50

<220>

<221> VARIANT

<222> (4)

<223> Xaa = Ala or Ser

55

<400> 3

EP 1 217 066 A1

Ala Thr Ser Xaa Leu Asp
1 5

5

10 <210> 4
 <211> 6
 <212> PRT
 <213> Homo sapiens

15 <400> 4
 Pro Leu Ser Ala Val Asp
 1 5

20 <210> 5
 <211> 6
 <212> PRT
 <213> Homo sapiens

25 <400> 5
 Ala Thr Ala Ala Val Asp
 1 5

30

35 <210> 6
 <211> 6
 <212> PRT
 <213> Homo sapiens

40 <400> 6
 Ala Thr Ala Ala Ile Asp
 1 5

45

50 <210> 7
 <211> 6
 <212> PRT
 <213> Homo sapiens

55 <400> 7
 Ala Thr Ala Asn Val Asp
 1 5

EP 1 217 066 A1

5 <210> 8
 <211> 6
 <212> PRT
 <213> Homo sapiens

10 <400> 8
 Pro Leu Ser Ala Leu Asp
 1 5

15 <210> 9
 <211> 6
 <212> PRT
 <213> Homo sapiens

20 <400> 9
 Ala Thr Ala Ala Met Asp
 1 5

25

30 <210> 10
 <211> 6
 <212> PRT
 <213> Homo sapiens

35 <400> 10
 Pro Leu Ala Ala Leu Asp
 1 5

40

45 <210> 11
 <211> 6
 <212> PRT
 <213> Homo sapiens

50 <400> 11
 Pro Phe Gly Tyr Leu Asp
 1 5

55 <210> 12
 <211> 6
 <212> PRT

EP 1217 066 A1

<213> Homo sapiens

<400> 12

Pro Ser Ala His Leu Asp

1 5

5

10

<210> 13

<211> 6

<212> PRT

15

<213> Homo sapiens

<400> 13

Pro Phe Ser Ala Leu Asp

1 5

20

<210> 14

25

<211> 6

<212> PRT

<213> Homo sapiens

30

<400> 14

Ala Thr Ala Ser Ile Asp

1 5

35

<210> 15

<211> 6

<212> PRT

40

<213> Homo sapiens

<400> 15

Pro Leu Ala Ala Val Asp

1 5

45

<210> 16

50

<211> 6

<212> PRT

<213> Homo sapiens

55

<400> 16

Pro Thr Ala Gly Val Asp

1 5

5

<210> 17
<211> 6
<212> PRT
10 <213> Homo sapiens

<400> 17
15 Pro Thr Thr Gly Met Asp
1 5

20

<210> 18
<211> 6
<212> PRT
25 <213> Homo sapiens

<400> 18
Pro Thr Ser Gly Met Asp
1 5

30

<210> 19
<211> 6
35 <212> PRT
<213> Homo sapiens

<400> 19
40 Pro Ser Thr Gly Met Asp
1 5

45

<210> 20
<211> 6
<212> PRT
50 <213> Homo sapiens

<400> 20
Pro Thr Ser Gly Val Asp
1 5

55

EP 1 217 066 A1

5 <210> 21
 <211> 6
 <212> PRT
 <213> Homo sapiens

10 <400> 21
 Pro Thr Ala Gly Leu Asp
 1 5

15 <210> 22
 <211> 6
 <212> PRT
 <213> Homo sapiens

20 <220>
 <221> VARIANT
 <222> (5)
 <223> Xaa = Val or Leu

25 <400> 22
 Pro Thr Ala Gly Xaa Asp
 1 5

30

35 <210> 23
 <211> 6
 <212> PRT
 <213> Homo sapiens

40 <220>
 <221> VARIANT
 <222> (5)
 <223> Xaa = Met or Val

45 <400> 23
 Pro Thr Ser Gly Xaa Asp
 1 5

50

55 <210> 24
 <211> 6
 <212> PRT
 <213> Homo sapiens

EP 1 217 066 A1

<220>
<221> VARIANT
5 <222> (2)
<223> Xaa = Thr or Ser

<400> 24
10 Pro Xaa Thr Gly Met Asp
1 5

15 <210> 25
<211> 8
<212> PRT
<213> Homo sapiens

20 <400> 25
Cys Thr Ser Ala Val Ser Ile Asp
1 5

25

<210> 26
<211> 8
30 <212> PRT
<213> Homo sapiens

<400> 26
35 Cys Thr Ser Ala Val Ser Val Asp
1 5

40

<210> 27
<211> 8
<212> PRT
<213> Homo sapiens

45 <400> 27
Ala Thr Ser Ala Leu Thr Glu Glu
1 5

50

<210> 28
<211> 6
55 <212> PRT
<213> Homo sapiens

EP 1 217 066 A1

<400> 28
Pro Ser Ala Tyr Leu Asp
1 5

5

10 <210> 29
<211> 6
<212> PRT
<213> Homo sapiens

15 <400> 29
Pro Thr Asn His Leu Asp
1 5

20

<210> 30
<211> 6
<212> PRT
<213> *Homo sapiens*

25

<400> 30
Pro Thr Asn Asn Leu Asp
1 5

30

35 <210> 31
<211> 6
<212> PRT
<213> Homo sapiens

40 <400> 31
Pro Thr Asn Met Leu Asp
1 5

45

<210> 32
<211> 6
<212> PRT
<213> *Homo sapiens*

50

<220>
<221> VARIANT
<222> (A)

55

EP 1 217 066 A1

<223> Xaa = His or Met

5 <400> 32

Pro Thr Asn Xaa Leu Asp

1 5

10

<210> 33

<211> 6

<212> PRT

15 <213> Homo sapiens

<220>

<221> VARIANT

<222> (4)

20 <223> Xaa = Asn or His

<400> 33

Pro Thr Asn Xaa Leu Asp

25 1 5

30

<210> 34

<211> 6

<212> PRT

<213> Homo sapiens

35

<400> 34

Pro Thr Ser Gly Leu Asp

1 5

40

<210> 35

<211> 6

<212> PRT

45 <213> Homo sapiens

<400> 35

Pro Thr Thr Gly Leu Asp

50 1 5

55

<210> 36

<211> 6

EP 1 217 066 A1

<212> PRT
<213> Homo sapiens

5 <220>
 <221> VARIANT
 <222> (3)
 <223> Xaa = Thr or Ser

10 <400> 36
 Pro Thr Xaa Gly Leu Asp
 1 5

15 <210> 37
 <211> 6
20 <212> PRT
 <213> Streptomyces lincolnensis

25 <400> 37
 Ala Thr Ala Ser Leu Asp
 1 5

30 <210> 38
 <211> 6
 <212> PRT
 <213> Streptomyces peucetius

35 <400> 38
 Ala Asp Gln Leu Ala Asp
 1 5

40 <210> 39
 <211> 6
45 <212> PRT
 <213> Streptomyces coelicolor

50 <400> 39
 Pro Thr Asn His Leu Ser
 1 5

55 <210> 40

EP 1 217 066 A1

<211> 6
<212> PRT
5 <213> *Schizosaccharomyces pombe*

<400> 40
10 Ser Thr Arg Gly Leu Asp
 1 5

15 <210> 41
<211> 6
<212> PRT
20 <213> *Schizosaccharomyces pombe*

<400> 41
25 Pro Thr Ser Gly Leu Asp
 1 5

30 <210> 42
<211> 6
<212> PRT
35 <213> *Candida albicans*

<400> 42
Ala Thr Arg Gly Leu Asp
35 1 5

40 <210> 43
<211> 6
<212> PRT
45 <213> *Leishmania tarentolae*

<400> 43
45 Ala Thr Ala Asn Ile Asp
 1 5

50 <210> 44
<211> 2261
<212> PRT
55 <213> *Homo sapiens*

EP 1 217 066 A1

<400> 44
Met Ala Cys Trp Pro Gln Leu Arg Leu Leu Leu Trp Lys Asn Leu Thr
1 5 10 15
5
Phe Arg Arg Arg Gln Thr Cys Gln Leu Leu Leu Glu Val Ala Trp Pro
20 25 30
10 Leu Phe Ile Phe Leu Ile Leu Ile Ser Val Arg Leu Ser Tyr Pro Pro
35 40 45
15 Tyr Glu Gln His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala
50 55 60
Gly Thr Leu Pro Trp Val Gln Gly Ile Ile Cys Asn Ala Asn Asn Pro
65 70 75 80
20 Cys Phe Arg Tyr Pro Thr Pro Gly Glu Ala Pro Gly Val Val Gly Asn
85 90 95
25 Phe Asn Lys Ser Ile Val Ala Arg Leu Phe Ser Asp Ala Arg Arg Leu
100 105 110
Leu Leu Tyr Ser Gln Lys Asp Thr Ser Met Lys Asp Met Arg Lys Val
115 120 125
30 Leu Arg Thr Leu Gln Gln Ile Lys Lys Ser Ser Ser Asn Leu Lys Leu
130 135 140
35 Gln Asp Phe Leu Val Asp Asn Glu Thr Phe Ser Gly Phe Leu Tyr His
145 150 155 160
Asn Leu Ser Leu Pro Lys Ser Thr Val Asp Lys Met Leu Arg Ala Asp
165 170 175
40 Val Ile Leu His Lys Val Phe Leu Gln Gly Tyr Gln Leu His Leu Thr
180 185 190
45 Ser Leu Cys Asn Gly Ser Lys Ser Glu Glu Met Ile Gln Leu Gly Asp
195 200 205
Gln Glu Val Ser Glu Leu Cys Gly Leu Pro Arg Glu Lys Leu Ala Ala
210 215 220
50 Ala Glu Arg Val Leu Arg Ser Asn Met Asp Ile Leu Lys Pro Ile Leu
225 230 235 240
55 Arg Thr Leu Asn Ser Thr Ser Pro Phe Pro Ser Lys Glu Leu Ala Glu
245 250 255

EP 1 217 066 A1

Ala Thr Lys Thr Leu Leu His Ser Leu Gly Thr Leu Ala Gln Glu Leu
260 265 270
5

Phe Ser Met Arg Ser Trp Ser Asp Met Arg Gln Glu Val Met Phe Leu
275 280 285

10 Thr Asn Val Asn Ser Ser Ser Ser Thr Gln Ile Tyr Gln Ala Val
290 295 300

Ser Arg Ile Val Cys Gly His Pro Glu Gly Gly Leu Lys Ile Lys
15 305 310 315 320

Ser Leu Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Leu Phe Gly Gly
325 330 335

20 Asn Gly Thr Glu Glu Asp Ala Glu Thr Phe Tyr Asp Asn Ser Thr Thr
340 345 350

Pro Tyr Cys Asn Asp Leu Met Lys Asn Leu Glu Ser Ser Pro Leu Ser
25 355 360 365

Arg Ile Ile Trp Lys Ala Leu Lys Pro Leu Leu Val Gly Lys Ile Leu
370 375 380

30 Tyr Thr Pro Asp Thr Pro Ala Thr Arg Gln Val Met Ala Glu Val Asn
385 390 395 400

Lys Thr Phe Gln Glu Leu Ala Val Phe His Asp Leu Glu Gly Met Trp
35 405 410 415

Glu Glu Leu Ser Pro Lys Ile Trp Thr Phe Met Glu Asn Ser Gln Glu
40 420 425 430

Met Asp Leu Val Arg Met Leu Leu Asp Ser Arg Asp Asn Asp His Phe
45 435 440 445

Trp Glu Gln Gln Leu Asp Gly Leu Asp Trp Thr Ala Gln Asp Ile Val
45 450 455 460

Ala Phe Leu Ala Lys His Pro Glu Asp Val Gln Ser Ser Asn Gly Ser
50 465 470 475 480

Val Tyr Thr Trp Arg Glu Ala Phe Asn Glu Thr Asn Gln Ala Ile Arg
485 490 495

55 Thr Ile Ser Arg Phe Met Glu Cys Val Asn Leu Asn Lys Leu Glu Pro
500 505 510

Ile Ala Thr Glu Val Trp Leu Ile Asn Lys Ser Met Glu Leu Leu Asp
 5 515 520 525
 Glu Arg Lys Phe Trp Ala Gly Ile Val Phe Thr Gly Ile Thr Pro Gly
 530 535 540
 Ser Ile Glu Leu Pro His His Val Lys Tyr Lys Ile Arg Met Asp Ile
 10 545 550 555 560
 Asp Asn Val Glu Arg Thr Asn Lys Ile Lys Asp Gly Tyr Trp Asp Pro
 15 565 570 575
 Gly Pro Arg Ala Asp Pro Phe Glu Asp Met Arg Tyr Val Trp Gly Gly
 580 585 590
 Phe Ala Tyr Leu Gln Asp Val Val Glu Gln Ala Ile Ile Arg Val Leu
 20 595 600 605
 Thr Gly Thr Glu Lys Lys Thr Gly Val Tyr Met Gln Gln Met Pro Tyr
 25 610 615 620
 Pro Cys Tyr Val Asp Asp Ile Phe Leu Arg Val Met Ser Arg Ser Met
 625 630 635 640
 Pro Leu Phe Met Thr Leu Ala Trp Ile Tyr Ser Val Ala Val Ile Ile
 30 645 650 655
 Lys Gly Ile Val Tyr Glu Lys Glu Ala Arg Leu Lys Glu Thr Met Arg
 35 660 665 670
 Ile Met Gly Leu Asp Asn Ser Ile Leu Trp Phe Ser Trp Phe Ile Ser
 675 680 685
 Ser Leu Ile Pro Leu Leu Val Ser Ala Gly Leu Leu Val Val Ile Leu
 40 690 695 700
 Lys Leu Gly Asn Leu Leu Pro Tyr Ser Asp Pro Ser Val Val Phe Val
 45 705 710 715 720
 Phe Leu Ser Val Phe Ala Val Val Thr Ile Leu Gln Cys Phe Leu Ile
 50 725 730 735
 Ser Thr Leu Phe Ser Arg Ala Asn Leu Ala Ala Ala Cys Gly Gly Ile
 740 745 750
 Ile Tyr Phe Thr Leu Tyr Leu Pro Tyr Val Leu Cys Val Ala Trp Gln
 55 755 760 765

EP 1 217 066 A1

Asp Tyr Val Gly Phe Thr Leu Lys Ile Phe Ala Ser Leu Leu Ser Pro
770 775 780

5

Val Ala Phe Gly Phe Gly Cys Glu Tyr Phe Ala Leu Phe Glu Glu Gln
785 790 795 800

10 Gly Ile Gly Val Gln Trp Asp Asn Leu Phe Glu Ser Pro Val Glu Glu
805 810 815

15 Asp Gly Phe Asn Leu Thr Thr Ser Val Ser Met Met Leu Phe Asp Thr
820 825 830

Phe Leu Tyr Gly Val Met Thr Trp Tyr Ile Glu Ala Val Phe Pro Gly
835 840 845

20 Gln Tyr Gly Ile Pro Arg Pro Trp Tyr Phe Pro Cys Thr Lys Ser Tyr
850 855 860

25 Trp Phe Gly Glu Glu Ser Asp Glu Lys Ser His Pro Gly Ser Asn Gln
865 870 875 880

Lys Arg Ile Ser Glu Ile Cys Met Glu Glu Glu Pro Thr His Leu Lys
885 890 895

30 Leu Gly Val Ser Ile Gln Asn Leu Val Lys Val Tyr Arg Asp Gly Met
900 905 910

35 Lys Val Ala Val Asp Gly Leu Ala Leu Asn Phe Tyr Glu Gly Gln Ile
915 920 925

40 Thr Ser Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Met Ser
930 935 940

Ile Leu Thr Gly Leu Phe Pro Pro Thr Ser Gly Thr Ala Tyr Ile Leu
945 950 955 960

45 Gly Lys Asp Ile Arg Ser Glu Met Ser Thr Ile Arg Gln Asn Leu Gly
965 970 975

50 Val Cys Pro Gln His Asn Val Leu Phe Asp Met Leu Thr Val Glu Glu
980 985 990

His Ile Trp Phe Tyr Ala Arg Leu Lys Gly Leu Ser Glu Lys His Val
995 1000 1005

55 Lys Ala Glu Met Glu Gln Met Ala Leu Asp Val Gly Leu Pro Ser Ser
1010 1015 1020

EP 1 217 066 A1

Lys Leu Lys Ser Lys Thr Ser Gln Leu Ser Gly Gly Met Gln Arg Lys
1025 1030 1035 1040
5

Leu Ser Val Ala Leu Ala Phe Val Gly Gly Ser Lys Val Val Ile Leu
1045 1050 1055

10 Asp Glu Pro Thr Ala Gly Val Asp Pro Tyr Ser Arg Arg Gly Ile Trp
1060 1065 1070

Glu Leu Leu Leu Lys Tyr Arg Gln Gly Arg Thr Ile Ile Leu Ser Thr
15 1075 1080 1085

His His Met Asp Glu Ala Asp Val Leu Gly Asp Arg Ile Ala Ile Ile
1090 1095 1100

20 Ser His Gly Lys Leu Cys Cys Val Gly Ser Ser Leu Phe Leu Lys Asn
1105 1110 1115 1120

Gln Leu Gly Thr Gly Tyr Tyr Leu Thr Leu Val Lys Lys Asp Val Glu
25 1125 1130 1135

Ser Ser Leu Ser Ser Cys Arg Asn Ser Ser Ser Thr Val Ser Tyr Leu
1140 1145 1150

30 Lys Lys Glu Asp Ser Val Ser Gln Ser Ser Ser Asp Ala Gly Leu Gly
1155 1160 1165

Ser Asp His Glu Ser Asp Thr Leu Thr Ile Asp Val Ser Ala Ile Ser
35 1170 1175 1180

Asn Leu Ile Arg Lys His Val Ser Glu Ala Arg Leu Val Glu Asp Ile
1185 1190 1195 1200

40 Gly His Glu Leu Thr Tyr Val Leu Pro Tyr Glu Ala Ala Lys Glu Gly
1205 1210 1215

Ala Phe Val Glu Leu Phe His Glu Ile Asp Asp Arg Leu Ser Asp Leu
45 1220 1225 1230

Gly Ile Ser Ser Tyr Gly Ile Ser Glu Thr Thr Leu Glu Glu Ile Phe
1235 1240 1245

50 Leu Lys Val Ala Glu Glu Ser Gly Val Asp Ala Glu Thr Ser Asp Gly
1250 1255 1260

Thr Leu Pro Ala Arg Arg Asn Arg Arg Ala Phe Gly Asp Lys Gln Ser
55 1265 1270 1275 1280

EP 1 217 066 A1

Cys Leu Arg Pro Phe Thr Glu Asp Asp Ala Ala Asp Pro Asn Asp Ser
5 1285 1290 1295

Asp Ile Asp Pro Glu Ser Arg Glu Thr Asp Leu Leu Ser Gly Met Asp
10 1300 1305 1310

Gly Lys Gly Ser Tyr Gln Val Lys Gly Trp Lys Leu Thr Gln Gln Gln
15 1315 1320 1325

Phe Val Ala Leu Leu Trp Lys Arg Leu Leu Ile Ala Arg Arg Ser Arg
1330 1335 1340

Lys Gly Phe Phe Ala Gln Ile Val Leu Pro Ala Val Phe Val Cys Ile
20 1345 1350 1355 1360

Ala Leu Val Phe Ser Leu Ile Val Pro Pro Phe Gly Lys Tyr Pro Ser
1365 1370 1375

Leu Glu Leu Gln Pro Trp Met Tyr Asn Glu Gln Tyr Thr Phe Val Ser
25 1380 1385 1390

Asn Asp Ala Pro Glu Asp Thr Gly Thr Leu Glu Leu Leu Asn Ala Leu
30 1395 1400 1405

Thr Lys Asp Pro Gly Phe Gly Thr Arg Cys Met Glu Gly Asn Pro Ile
1410 1415 1420

Pro Asp Thr Pro Cys Gln Ala Gly Glu Glu Trp Thr Thr Ala Pro
35 1425 1430 1435 1440

Val Pro Gln Thr Ile Met Asp Leu Phe Gln Asn Gly Asn Trp Thr Met
40 1445 1450 1455

Gln Asn Pro Ser Pro Ala Cys Gln Cys Ser Ser Asp Lys Ile Lys Lys
45 1460 1465 1470

Met Leu Pro Val Cys Pro Pro Gly Ala Gly Gly Leu Pro Pro Pro Gln
1475 1480 1485

Arg Lys Gln Asn Thr Ala Asp Ile Leu Gln Asp Leu Thr Gly Arg Asn
50 1490 1495 1500

Ile Ser Asp Tyr Leu Val Lys Thr Tyr Val Gln Ile Ile Ala Lys Ser
1505 1510 1515 1520

Leu Lys Asn Lys Ile Trp Val Asn Glu Phe Arg Tyr Gly Gly Phe Ser
55 1525 1530 1535

EP 1 217 066 A1

Leu Gly Val Ser Asn Thr Gln Ala Leu Pro Pro Ser Gln Glu Val Asn
 1540 1545 1550
 5 Asp Ala Thr Lys Gln Met Lys Lys His Leu Lys Leu Ala Lys Asp Ser
 1555 1560 1565
 10 Ser Ala Asp Arg Phe Leu Asn Ser Leu Gly Arg Phe Met Thr Gly Leu
 1570 1575 1580
 15 Asp Thr Arg Asn Asn Val Lys Val Trp Phe Asn Asn Lys Gly Trp His
 1585 1590 1595 1600
 15 Ala Ile Ser Ser Phe Leu Asn Val Ile Asn Asn Ala Ile Leu Arg Ala
 1605 1610 1615
 20 Asn Leu Gln Lys Gly Glu Asn Pro Ser His Tyr Gly Ile Thr Ala Phe
 1620 1625 1630
 25 Asn His Pro Leu Asn Leu Thr Lys Gln Gln Leu Ser Glu Val Ala Pro
 1635 1640 1645
 Met Thr Thr Ser Val Asp Val Leu Val Ser Ile Cys Val Ile Phe Ala
 1650 1655 1660
 30 Met Ser Phe Val Pro Ala Ser Phe Val Val Phe Leu Ile Gln Glu Arg
 1665 1670 1675 1680
 Val Ser Lys Ala Lys His Leu Gln Phe Ile Ser Gly Val Lys Pro Val
 35 1685 1690 1695
 Ile Tyr Trp Leu Ser Asn Phe Val Trp Asp Met Cys Asn Tyr Val Val
 1700 1705 1710
 40 Pro Ala Thr Leu Val Ile Ile Phe Ile Cys Phe Gln Gln Lys Ser
 1715 1720 1725
 45 Tyr Val Ser Ser Thr Asn Leu Pro Val Leu Ala Leu Leu Leu Leu
 1730 1735 1740
 Tyr Gly Trp Ser Ile Thr Pro Leu Met Tyr Pro Ala Ser Phe Val Phe
 1745 1750 1755 1760
 50 Lys Ile Pro Ser Thr Ala Tyr Val Val Leu Thr Ser Val Asn Leu Phe
 1765 1770 1775
 55 Ile Gly Ile Asn Gly Ser Val Ala Thr Phe Val Leu Glu Leu Phe Thr
 1780 1785 1790

EP 1 217 066 A1

Asp Asn Lys Leu Asn Asn Ile Asn Asp Ile Leu Lys Ser Val Phe Leu
1795 1800 1805

5 Ile Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile Asp Met Val Lys
1810 1815 1820

10 Asn Gln Ala Met Ala Asp Ala Leu Glu Arg Phe Gly Glu Asn Arg Phe
1825 1830 1835 1840

15 Val Ser Pro Leu Ser Trp Asp Leu Val Gly Arg Asn Leu Phe Ala Met
1845 1850 1855

20 Ala Val Glu Gly Val Val Phe Phe Leu Ile Thr Val Leu Ile Gln Tyr
1860 1865 1870

25 Arg Phe Phe Ile Arg Pro Arg Pro Val Asn Ala Lys Leu Ser Pro Leu
1875 1880 1885

30 Asn Asp Glu Asp Glu Asp Val Arg Arg Glu Arg Gln Arg Ile Leu Asp
1890 1895 1900

Gly Gly Gly Gln Asn Asp Ile Leu Glu Ile Lys Glu Leu Thr Lys Ile
1905 1910 1915 1920

35 Tyr Arg Arg Lys Arg Lys Pro Ala Val Asp Arg Ile Cys Val Gly Ile
1925 1930 1935

Pro Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys
1940 1945 1950

40 Ser Ser Thr Phe Lys Met Leu Thr Gly Asp Thr Thr Val Thr Arg Gly
1955 1960 1965

45 Asp Ala Phe Leu Asn Arg Asn Ser Ile Leu Ser Asn Ile His Glu Val
1970 1975 1980

His Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Thr Glu Leu
1985 1990 1995 2000

Leu Thr Gly Arg Glu His Val Glu Phe Phe Ala Leu Leu Arg Gly Val
2005 2010 2015

50 Pro Glu Lys Glu Val Gly Lys Val Gly Glu Trp Ala Ile Arg Lys Leu
2020 2025 2030

55 Gly Leu Val Lys Tyr Gly Glu Lys Tyr Ala Gly Asn Tyr Ser Gly Gly
2035 2040 2045

EP 1 217 066 A1

Asn Lys Arg Lys Leu Ser Thr Ala Met Ala Leu Ile Gly Gly Pro Pro
2050 2055 2060

5 Val Val Phe Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Lys Ala Arg
2065 2070 2075 2080

10 Arg Phe Leu Trp Asn Cys Ala Leu Ser Val Val Lys Glu Gly Arg Ser
2085 2090 2095

Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr
2100 2105 2110

15 Arg Met Ala Ile Met Val Asn Gly Arg Phe Arg Cys Leu Gly Ser Val
2115 2120 2125

20 Gln His Leu Lys Asn Arg Phe Gly Asp Gly Tyr Thr Ile Val Val Arg
2130 2135 2140

25 Ile Ala Gly Ser Asn Pro Asp Leu Lys Pro Val Gln Asp Phe Phe Gly
2145 2150 2155 2160

Leu Ala Phe Pro Gly Ser Val Pro Lys Glu Lys His Arg Asn Met Leu
2165 2170 2175

30 Gln Tyr Gln Leu Pro Ser Ser Leu Ser Ser Leu Ala Arg Ile Phe Ser
2180 2185 2190

35 Ile Leu Ser Gln Ser Lys Lys Arg Leu His Ile Glu Asp Tyr Ser Val
2195 2200 2205

Ser Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Asp Gln
2210 2215 2220

40 Ser Asp Asp Asp His Leu Lys Asp Leu Ser Leu His Lys Asn Gln Thr
2225 2230 2235 2240

45 Val Val Asp Val Ala Val Leu Thr Ser Phe Leu Gln Asp Glu Lys Val
2245 2250 2255

Lys Glu Ser Tyr Val
2260

50

<210> 45

55 <211> 2436

<212> PRT

EP 1 217 066 A1

<213> Homo sapiens

5 <400> 45
Met Gly Phe Leu His Gln Leu Gln Leu Leu Leu Trp Lys Asn Val Thr
1 5 10 15

10 Leu Lys Arg Arg Ser Pro Trp Val Leu Ala Phe Glu Ile Phe Ile Pro
20 25 30

15 Leu Val Leu Phe Phe Ile Leu Leu Gly Leu Arg Gln Lys Lys Pro Thr
35 40 45

20 Ile Ser Val Lys Glu Val Pro Phe Tyr Thr Ala Ala Pro Leu Thr Ser
50 55 60

25 Ala Gly Ile Leu Pro Val Met Gln Ser Leu Cys Pro Asp Gly Gln Arg
65 70 75 80

30 Asp Glu Phe Gly Phe Leu Gln Tyr Ala Asn Ser Thr Val Thr Gln Leu
85 90 95

35 Leu Glu Arg Leu Asp Arg Val Val Glu Glu Gly Asn Leu Phe Asp Pro
100 105 110

40 Ala Arg Pro Ser Leu Gly Ser Glu Leu Glu Ala Leu Arg Gln His Leu
115 120 125

45 Glu Ala Leu Ser Ala Gly Pro Gly Thr Ser Gly Ser His Leu Asp Arg
130 135 140

50 Ser Thr Val Ser Ser Phe Ser Leu Asp Ser Val Ala Arg Asn Pro Gln
145 150 155 160

55 Glu Leu Trp Arg Phe Leu Thr Gln Asn Leu Ser Leu Pro Asn Ser Thr
165 170 175

60 Ala Gln Ala Leu Leu Ala Ala Arg Val Asp Pro Pro Glu Val Tyr His
180 185 190

65 Leu Leu Phe Gly Pro Ser Ser Ala Leu Asp Ser Gln Ser Gly Leu His
195 200 205

70 Lys Gly Gln Glu Pro Trp Ser Arg Leu Gly Gly Asn Pro Leu Phe Arg
210 215 220

75 Met Glu Glu Leu Leu Ala Pro Ala Leu Leu Glu Gln Leu Thr Cys
225 230 235 240

EP 1 217 066 A1

Thr Pro Gly Ser Gly Glu Leu Gly Arg Ile Leu Thr Val Pro Glu Ser
245 250 255

5 Gln Lys Gly Ala Leu Gln Gly Tyr Arg Asp Ala Val Cys Ser Gly Gln
260 265 270

10 Ala Ala Ala Arg Ala Arg Arg Phe Ser Gly Leu Ser Ala Glu Leu Arg
275 280 285

15 Asn Gln Leu Asp Val Ala Lys Val Ser Gln Gln Leu Gly Leu Asp Ala
290 295 300

20 Pro Asn Gly Ser Asp Ser Ser Pro Gln Ala Pro Pro Pro Arg Arg Leu
305 310 315 320

Gln Ala Leu Leu Gly Asp Leu Leu Asp Ala Gln Lys Val Leu Gln Asp
325 330 335

25 Val Asp Val Leu Ser Ala Leu Ala Leu Leu Pro Gln Gly Ala Cys
340 345 350

30 Thr Gly Arg Thr Pro Gly Pro Pro Ala Ser Gly Ala Gly Gly Ala Ala
355 360 365

Asn Gly Thr Gly Ala Gly Ala Val Met Gly Pro Asn Ala Thr Ala Glu
370 375 380

35 Glu Gly Ala Pro Ser Ala Ala Leu Ala Thr Pro Asp Thr Leu Gln
385 390 395 400

Gly Gln Cys Ser Ala Phe Val Gln Leu Trp Ala Gly Leu Gln Pro Ile
405 410 415

40 Leu Cys Gly Asn Asn Arg Thr Ile Glu Pro Glu Ala Leu Arg Arg Gly
420 425 430

45 Asn Met Ser Ser Leu Gly Phe Thr Ser Lys Glu Gln Arg Asn Leu Gly
435 440 445

Leu Leu Val His Leu Met Thr Ser Asn Pro Lys Ile Leu Tyr Ala Pro
450 455 460

50 Ala Gly Ser Glu Val Asp Arg Val Ile Leu Lys Ala Asn Glu Thr Phe
465 470 475 480

55 Ala Phe Val Gly Asn Val Thr His Tyr Ala Gln Val Trp Leu Asn Ile
485 490 495

EP 1 217 066 A1

Ser Ala Glu Ile Arg Ser Phe Leu Glu Gln Gly Arg Leu Gln Gln His
 500 505 510
 5 Leu Arg Trp Leu Gln Gln Tyr Val Ala Glu Leu Arg Leu His Pro Glu
 515 520 525
 10 Ala Leu Asn Leu Ser Leu Asp Glu Leu Pro Pro Ala Leu Arg Gln Asp
 530 535 540
 Asn Phe Ser Leu Pro Ser Gly Met Ala Leu Leu Gln Gln Leu Asp Thr
 545 550 555 560
 15 Ile Asp Asn Ala Ala Cys Gly Trp Ile Gln Phe Met Ser Lys Val Ser
 565 570 575
 20 Val Asp Ile Phe Lys Gly Phe Pro Asp Glu Glu Ser Ile Val Asn Tyr
 580 585 590
 Thr Leu Asn Gln Ala Tyr Gln Asp Asn Val Thr Val Phe Ala Ser Val
 595 600 605
 25 Ile Phe Gln Thr Arg Lys Asp Gly Ser Leu Pro Pro His Val His Tyr
 610 615 620
 30 Lys Ile Arg Gln Asn Ser Ser Phe Thr Glu Lys Thr Asn Glu Ile Arg
 625 630 635 640
 Arg Ala Tyr Trp Arg Pro Gly Pro Asn Thr Gly Gly Arg Phe Tyr Phe
 645 650 655
 35 Leu Tyr Gly Phe Val Trp Ile Gln Asp Met Met Glu Arg Ala Ile Ile
 660 665 670
 40 Asp Thr Phe Val Gly His Asp Val Val Glu Pro Gly Ser Tyr Val Gln
 675 680 685
 Met Phe Pro Tyr Pro Cys Tyr Thr Arg Asp Asp Phe Leu Phe Val Ile
 690 695 700
 45 Glu His Met Met Pro Leu Cys Met Val Ile Ser Trp Val Tyr Ser Val
 705 710 715 720
 50 Ala Met Thr Ile Gln His Ile Val Ala Glu Lys Glu His Arg Leu Lys
 725 730 735
 55 Glu Val Met Lys Thr Met Gly Leu Asn Asn Ala Val His Trp Val Ala
 740 745 750

EP 1 217 066 A1

Trp Phe Ile Thr Gly Phe Val Gln Leu Ser Ile Ser Val Thr Ala Leu
755 760 765

5 Thr Ala Ile Leu Lys Tyr Gly Gln Val Leu Met His Ser His Val Val
770 775 780

Ile Ile Trp Leu Phe Leu Ala Val Tyr Ala Val Ala Thr Ile Met Phe
10 785 790 795 800

Cys Phe Leu Val Ser Val Leu Tyr Ser Lys Ala Lys Leu Ala Ser Ala
805 810 815

15 Cys Gly Gly Ile Ile Tyr Phe Leu Ser Tyr Val Pro Tyr Met Tyr Val
820 825 830

Ala Ile Arg Glu Glu Val Ala His Asp Lys Ile Thr Ala Phe Glu Lys
20 835 840 845

Cys Ile Ala Ser Leu Met Ser Thr Thr Ala Phe Gly Leu Gly Ser Lys
850 855 860

25 Tyr Phe Ala Leu Tyr Glu Val Ala Gly Val Gly Ile Gln Trp His Thr
865 870 875 880

Phe Ser Gln Ser Pro Val Glu Gly Asp Asp Phe Asn Leu Leu Ala
30 885 890 895

Val Thr Met Leu Met Val Asp Ala Val Val Tyr Gly Ile Leu Thr Trp
35 900 905 910

Tyr Ile Glu Ala Val His Pro Gly Met Tyr Gly Leu Pro Arg Pro Trp
915 920 925

40 Tyr Phe Pro Leu Gln Lys Ser Tyr Trp Leu Gly Ser Gly Arg Thr Glu
930 935 940

Ala Trp Glu Trp Ser Trp Pro Trp Ala Arg Thr Pro Arg Leu Ser Val
45 945 950 955 960

Met Glu Glu Asp Gln Ala Cys Ala Met Glu Ser Arg Arg Phe Glu Glu
965 970 975

50 Thr Arg Gly Met Glu Glu Glu Pro Thr His Leu Pro Leu Val Val Cys
980 985 990

Val Asp Lys Leu Thr Lys Val Tyr Lys Asp Asp Lys Lys Leu Ala Leu
55 995 1000 1005

EP 1217066 A1

Asn Lys Leu Ser Leu Asn Leu Tyr Glu Asn Gln Val Val Ser Phe Leu
1010 1015 1020

5 Gly His Asn Gly Ala Gly Lys Thr Thr Thr Met Ser Ile Leu Thr Gly
1025 1030 1035 1040

Leu Phe Pro Pro Thr Ser Gly Ser Ala Thr Ile Tyr Gly His Asp Ile
10 1045 1050 1055

Arg Thr Glu Met Asp Glu Ile Arg Lys Asn Leu Gly Met Cys Pro Gln
1060 1065 1070

15 His Asn Val Leu Phe Asp Arg Leu Thr Val Glu Glu His Leu Trp Phe
1075 1080 1085

Tyr Ser Arg Leu Lys Ser Met Ala Gln Glu Glu Ile Arg Arg Glu Met
20 1090 1095 1100

Asp Lys Met Ile Glu Asp Leu Glu Leu Ser Asn Lys Arg His Ser Leu
1105 1110 1115 1120

25 Val Gln Thr Leu Ser Gly Gly Met Lys Arg Lys Leu Ser Val Ala Ile
1125 1130 1135

Ala Phe Val Gly Gly Ser Arg Ala Ile Ile Leu Asp Glu Pro Thr Ala
30 1140 1145 1150

Gly Val Asp Pro Tyr Ala Arg Arg Ala Ile Trp Asp Leu Ile Leu Lys
35 1155 1160 1165

Tyr Lys Pro Gly Arg Thr Ile Leu Leu Ser Thr His His Met Asp Glu
1170 1175 1180

40 Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ser His Gly Lys Leu
1185 1190 1195 1200

Lys Cys Cys Gly Ser Pro Leu Phe Leu Lys Gly Thr Tyr Asp Gly
45 1205 1210 1215

Tyr Arg Leu Thr Leu Val Lys Arg Pro Ala Glu Pro Gly Gly Pro Gln
1220 1225 1230

50 Glu Pro Gly Leu Ala Ser Ser Pro Pro Gly Arg Ala Pro Leu Ser Ser
1235 1240 1245

Cys Ser Glu Leu Gln Val Ser Gln Phe Ile Arg Lys His Val Ala Ser
55 1250 1255 1260

EP 1 217 066 A1

Cys Leu Leu Val Ser Asp Thr Ser Thr Glu Leu Ser Tyr Ile Leu Pro
1265 1270 1275 1280

5 Ser Glu Ala Ala Lys Lys Gly Ala Phe Glu Arg Leu Phe Gln His Leu
1285 1290 1295

Glu Arg Ser Leu Asp Ala Leu His Leu Ser Ser Phe Gly Leu Met Asp
10 1300 1305 1310

Thr Thr Leu Glu Glu Val Phe Leu Lys Val Ser Glu Glu Asp Gln Ser
1315 1320 1325

15 Leu Glu Asn Ser Glu Ala Asp Val Lys Glu Ser Arg Lys Asp Val Leu
1330 1335 1340

Pro Gly Ala Glu Gly Pro Ala Ser Gly Glu Gly His Ala Gly Asn Leu
20 1345 1350 1355 1360

Ala Arg Cys Ser Glu Leu Thr Gln Ser Gln Ala Ser Leu Gln Ser Ala
1365 1370 1375

25 Ser Ser Val Gly Ser Ala Arg Gly Asp Glu Gly Ala Gly Tyr Thr Asp
1380 1385 1390

Val Tyr Gly Asp Tyr Arg Pro Leu Phe Asp Asn Pro Gln Asp Pro Asp
30 1395 1400 1405

Asn Val Ser Leu Gln Glu Val Glu Ala Glu Ala Leu Ser Arg Val Gly
35 1410 1415 1420

Gln Gly Ser Arg Lys Leu Asp Gly Gly Trp Leu Lys Val Arg Gln Phe
1425 1430 1435 1440

His Gly Leu Leu Val Lys Arg Phe His Cys Ala Arg Arg Asn Ser Lys
40 1445 1450 1455

Ala Leu Phe Ser Gln Ile Leu Leu Pro Ala Phe Phe Val Cys Val Ala
45 1460 1465 1470

Met Thr Val Ala Leu Ser Val Pro Glu Ile Gly Asp Leu Pro Pro Leu
1475 1480 1485

50 Val Leu Ser Pro Ser Gln Tyr His Asn Tyr Thr Gln Pro Arg Gly Asn
1490 1495 1500

Phe Ile Pro Tyr Ala Asn Glu Glu Arg Arg Glu Tyr Arg Leu Arg Leu
55 1505 1510 1515 1520

EP 1 217 066 A1

Ser Pro Asp Ala Ser Pro Gln Gln Leu Val Ser Thr Phe Arg Leu Pro
1525 1530 1535

5 Ser Gly Val Gly Ala Thr Cys Val Leu Lys Ser Pro Ala Asn Gly Ser
1540 1545 1550

Leu Gly Pro Thr Leu Asn Leu Ser Ser Gly Glu Ser Arg Leu Leu Ala
10 1555 1560 1565

Ala Arg Phe Phe Asp Ser Met Cys Leu Glu Ser Phe Thr Gln Gly Leu
1570 1575 1580

15 Pro Leu Ser Asn Phe Val Pro Pro Pro Ser Pro Ala Pro Ser Asp
1585 1590 1595 1600

Ser Pro Ala Ser Pro Asp Glu Asp Leu Gln Ala Trp Asn Val Ser Leu
20 1605 1610 1615

Pro Pro Thr Ala Gly Pro Glu Met Trp Thr Ser Ala Pro Ser Leu Pro
1620 1625 1630

25 Arg Leu Val Arg Glu Pro Val Arg Cys Thr Cys Ser Ala Gln Gly Thr
1635 1640 1645

Gly Phe Ser Cys Pro Ser Ser Val Gly Gly His Pro Pro Gln Met Arg
30 1650 1655 1660

Val Val Thr Gly Asp Ile Leu Thr Asp Ile Thr Gly His Asn Val Ser
1665 1670 1675 1680

35 Glu Tyr Leu Leu Phe Thr Ser Asp Arg Phe Arg Leu His Arg Tyr Gly
1685 1690 1695

Ala Ile Thr Phe Gly Asn Val Leu Lys Ser Ile Pro Ala Ser Phe Gly
40 1700 1705 1710

Thr Arg Ala Pro Pro Met Val Arg Lys Ile Ala Val Arg Arg Ala Ala
45 1715 1720 1725

Gln Val Phe Tyr Asn Asn Lys Gly Tyr His Ser Met Pro Thr Tyr Leu
1730 1735 1740

Asn Ser Leu Asn Asn Ala Ile Leu Arg Ala Asn Leu Pro Lys Ser Lys
50 1745 1750 1755 1760

Gly Asn Pro Ala Ala Tyr Gly Ile Thr Val Thr Asn His Pro Met Asn
55 1765 1770 1775

EP 1 217 066 A1

Lys Thr Ser Ala Ser Leu Ser Leu Asp Tyr Leu Leu Gln Gly Thr Asp
1780 1785 1790

5 Val Val Ile Ala Ile Phe Ile Ile Val Ala Met Ser Phe Val Pro Ala
1795 1800 1805

Ser Phe Val Val Phe Leu Val Ala Glu Lys Ser Thr Lys Ala Lys His
10 1810 1815 1820

Leu Gln Phe Val Ser Gly Cys Asn Pro Ile Ile Tyr Trp Leu Ala Asn
1825 1830 1835 1840

15 Tyr Val Trp Asp Met Leu Asn Tyr Leu Val Pro Ala Thr Cys Cys Val
1845 1850 1855

Ile Ile Leu Phe Val Phe Asp Leu Pro Ala Tyr Thr Ser Pro Thr Asn
20 1860 1865 1870

Phe Pro Ala Val Leu Ser Leu Phe Leu Leu Tyr Gly Trp Ser Ile Thr
1875 1880 1885

25 Pro Ile Met Tyr Pro Ala Ser Phe Trp Phe Glu Val Pro Ser Ser Ala
1890 1895 1900

Tyr Val Phe Leu Ile Val Ile Asn Leu Phe Ile Gly Ile Thr Ala Thr
30 1905 1910 1915 1920

Val Ala Thr Phe Leu Leu Gln Leu Phe Glu His Asp Lys Asp Leu Lys
35 1925 1930 1935

Val Val Asn Ser Tyr Leu Lys Ser Cys Phe Leu Ile Phe Pro Asn Tyr
1940 1945 1950

40 Asn Leu Gly His Gly Leu Met Glu Met Ala Tyr Asn Glu Tyr Ile Asn
1955 1960 1965

Glu Tyr Tyr Ala Lys Ile Gly Gln Phe Asp Lys Met Lys Ser Pro Phe
45 1970 1975 1980

Glu Trp Asp Ile Val Thr Arg Gly Leu Val Ala Met Ala Val Glu Gly
1985 1990 1995 2000

50 Val Val Gly Phe Leu Leu Thr Ile Met Cys Gln Tyr Asn Phe Leu Arg
2005 2010 2015

Arg Pro Gln Arg Met Pro Val Ser Thr Lys Pro Val Glu Asp Asp Val
55 2020 2025 2030

EP 1 217 066 A1

Asp Val Ala Ser Glu Arg Gln Arg Val Leu Arg Gly Asp Ala Asp Asn
 2035 2040 2045

5 Asp Met Val Lys Ile Glu Asn Leu Thr Lys Val Tyr Lys Ser Arg Lys
 2050 2055 2060

10 Ile Gly Arg Ile Leu Ala Val Asp Arg Leu Cys Leu Gly Val Arg Pro
 2065 2070 2075 2080

Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Ser
 2085 2090 2095

15 Thr Phe Lys Met Leu Thr Gly Asp Glu Ser Thr Thr Gly Gly Glu Ala
 2100 2105 2110

20 Phe Val Asn Gly His Ser Val Leu Lys Glu Leu Leu Gln Val Gln Gln
 2115 2120 2125

Ser Leu Gly Tyr Cys Pro Gln Cys Asp Ala Leu Phe Asp Glu Leu Thr
 2130 2135 2140

25 Ala Arg Glu His Leu Gln Leu Tyr Thr Arg Leu Arg Gly Ile Ser Trp
 2145 2150 2155 2160

30 Lys Asp Glu Ala Arg Val Val Lys Trp Ala Leu Glu Lys Leu Glu Leu
 2165 2170 2175

Thr Lys Tyr Ala Asp Lys Pro Ala Gly Thr Tyr Ser Gly Gly Asn Lys
 2180 2185 2190

35 Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly Tyr Pro Ala Phe Ile
 2195 2200 2205

40 Phe Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Lys Ala Arg Arg Phe
 2210 2215 2220

45 Leu Trp Asn Leu Ile Leu Asp Leu Ile Lys Thr Gly Arg Ser Val Val
 2225 2230 2235 2240

Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu
 2245 2250 2255

50 Ala Ile Met Val Asn Gly Arg Leu Arg Cys Leu Gly Ser Ile Gln His
 2260 2265 2270

55 Leu Lys Asn Arg Phe Gly Asp Gly Tyr Met Ile Thr Val Arg Thr Lys
 2275 2280 2285

EP 1 217 066 A1

Ser Ser Gln Ser Val Lys Asp Val Val Arg Phe Phe Asn Arg Asn Phe
2290 2295 2300

5 Pro Glu Ala Met Leu Lys Glu Arg His His Thr Lys Val Gln Tyr Gln
2305 2310 2315 2320

10 Leu Lys Ser Glu His Ile Ser Leu Ala Gln Val Phe Ser Lys Met Glu
2325 2330 2335

Gln Val Ser Gly Val Leu Gly Ile Glu Asp Tyr Ser Val Ser Gln Thr
2340 2345 2350

15 Thr Leu Asp Asn Val Phe Val Asn Phe Ala Lys Lys Gln Ser Asp Asn
2355 2360 2365

20 Leu Glu Gln Gln Glu Thr Glu Pro Pro Ser Ala Leu Gln Ser Pro Leu
2370 2375 2380

Gly Cys Leu Leu Ser Leu Leu Arg Pro Arg Ser Ala Pro Thr Glu Leu
2385 2390 2395 2400

25 Arg Ala Leu Val Ala Asp Glu Pro Glu Asp Leu Asp Thr Glu Asp Glu
2405 2410 2415

30 Gly Leu Ile Ser Phe Glu Glu Glu Arg Ala Gln Leu Ser Phe Asn Thr
2420 2425 2430

Asp Thr Leu Cys
2435

35

<210> 46
40 <211> 1704
<212> PRT
<213> Homo sapiens

45 <400> 46
Met Ala Val Leu Arg Gln Leu Ala Leu Leu Leu Trp Lys Asn Tyr Thr
1 5 10 15

50 Leu Gln Lys Arg Lys Val Leu Val Thr Val Leu Glu Leu Phe Leu Pro
20 25 30

Leu Leu Phe Pro Gly Ile Leu Ile Trp Leu Arg Leu Lys Ile Gln Ser
35 40 45

55 Glu Asn Val Pro Asn Ala Thr Ile Tyr Pro Gly Gln Ser Ile Gln Glu

EP 1 217 066 A1

	50	55	60
5	Leu Pro Leu Phe Phe Thr Phe Pro Pro Pro Gly Asp Thr Trp Glu Leu		
	65	70	75
	Ala Tyr Ile Pro Ser His Ser Asp Ala Ala Lys Thr Val Thr Glu Thr		
10	85	90	95
	Val Arg Arg Ala Leu Val Ile Asn Met Arg Val Arg Gly Phe Pro Ser		
	100	105	110
15	Glu Lys Asp Phe Glu Asp Tyr Ile Arg Tyr Asp Asn Cys Ser Ser Ser		
	115	120	125
	Val Leu Ala Ala Val Val Phe Glu His Pro Phe Asn His Ser Lys Glu		
20	130	135	140
	Pro Leu Pro Leu Ala Val Lys Tyr His Leu Arg Phe Ser Tyr Thr Arg		
	145	150	155
	Arg Asn Tyr Met Trp Thr Gln Thr Gly Ser Phe Phe Leu Lys Glu Thr		
25	165	170	175
	Glu Gly Trp His Thr Thr Ser Leu Phe Pro Leu Phe Pro Asn Pro Gly		
30	180	185	190
	Pro Arg Glu Leu Thr Ser Pro Asp Gly Gly Glu Pro Gly Tyr Ile Arg		
	195	200	205
35	Glu Gly Phe Leu Ala Val Gln His Ala Val Asp Arg Ala Ile Met Glu		
	210	215	220
	Tyr His Ala Asp Ala Ala Thr Arg Gln Leu Phe Gln Arg Leu Thr Val		
40	225	230	235
	240		
	Thr Ile Lys Arg Phe Pro Tyr Pro Pro Phe Ile Ala Asp Pro Phe Leu		
	245	250	255
45	Val Ala Ile Gln Tyr Gln Leu Pro Leu Leu Leu Leu Ser Phe Thr		
	260	265	270
	Tyr Thr Ala Leu Thr Ile Ala Arg Ala Val Val Gln Glu Lys Glu Arg		
50	275	280	285
	Arg Leu Lys Glu Tyr Met Arg Met Met Gly Leu Ser Ser Trp Leu His		
	290	295	300
55	Trp Ser Ala Trp Phe Leu Leu Phe Phe Leu Phe Leu Ile Ala Ala		

EP 1 217 066 A1

305 310 315 320
5 Ser Phe Met Thr Leu Leu Phe Cys Val Lys Val Lys Pro Asn Val Ala
 325 330 335

Val Leu Ser Arg Ser Asp Pro Ser Leu Val Leu Ala Phe Leu Leu Cys
10 340 345 350
 Phe Ala Ile Ser Thr Ile Ser Phe Ser Phe Met Val Ser Thr Phe Phe
 355 360 365

15 Ser Lys Ala Asn Met Ala Ala Ala Phe Gly Gly Phe Leu Tyr Phe Phe
 370 375 380

Thr Tyr Ile Pro Tyr Phe Phe Val Ala Pro Arg Tyr Asn Trp Met Thr
20 385 390 395 400
 Leu Ser Gln Lys Leu Cys Ser Cys Leu Leu Ser Asn Val Ala Met Ala
 405 410 415

25 Met Gly Ala Gln Leu Ile Gly Lys Phe Glu Ala Lys Gly Met Gly Ile
 420 425 430

Gln Trp Arg Asp Leu Leu Ser Pro Val Asn Val Asp Asp Asp Phe Cys
30 435 440 445

Phe Gly Gln Val Leu Gly Met Leu Leu Leu Asp Ser Val Leu Tyr Gly
 450 455 460

35 Leu Val Thr Trp Tyr Met Glu Ala Val Phe Pro Gly Gln Phe Gly Val
 465 470 475 480

Pro Gln Pro Trp Tyr Phe Phe Ile Met Pro Ser Tyr Trp Cys Gly Lys
40 485 490 495

Pro Arg Ala Val Ala Gly Lys Glu Glu Glu Asp Ser Asp Pro Glu Lys
 500 505 510

45 Ala Leu Arg Asn Glu Tyr Phe Glu Ala Glu Pro Glu Asp Leu Val Ala
 515 520 525

Gly Ile Lys Ile Lys His Leu Ser Lys Val Phe Arg Val Gly Asn Lys
50 530 535 540

Asp Arg Ala Ala Val Arg Asp Leu Asn Leu Asn Leu Tyr Glu Gly Gln
 545 550 555 560

55 Ile Thr Val Leu Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu

EP 1 217 066 A1

	565	570	575
5	Ser Met Leu Thr Gly Leu Phe Pro Pro Thr Ser Gly Arg Ala Tyr Ile 580	585	590
	Ser Gly Tyr Glu Ile Ser Gln Asp Met Val Gln Ile Arg Lys Ser Leu 595	600	605
10	Gly Leu Cys Pro Gln His Asp Ile Leu Phe Asp Asn Leu Thr Val Ala 610	615	620
15	Glu His Leu Tyr Phe Tyr Ala Gln Leu Lys Gly Leu Ser Arg Gln Lys 625	630	635
	Cys Pro Glu Glu Val Lys Gln Met Leu His Ile Ile Gly Leu Glu Asp 645	650	655
20	Lys Trp Asn Ser Arg Ser Arg Phe Leu Ser Gly Gly Met Arg Arg Lys 660	665	670
	Leu Ser Ile Gly Ile Ala Leu Ile Ala Gly Ser Lys Val Leu Ile Leu 675	680	685
25	Asp Glu Pro Thr Ser Gly Met Asp Ala Ile Ser Arg Arg Ala Ile Trp 690	695	700
30	Asp Leu Leu Gln Arg Gln Lys Ser Asp Arg Thr Ile Val Leu Thr Thr 705	710	715
	His Phe Met Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Met 725	730	735
35	Ala Lys Gly Glu Leu Gln Cys Cys Gly Ser Ser Leu Phe Leu Lys Gln 740	745	750
40	Lys Tyr Gly Ala Gly Tyr His Met Thr Leu Val Lys Glu Pro His Cys 755	760	765
	Asn Pro Glu Asp Ile Ser Gln Leu Val His His His Val Pro Asn Ala 770	775	780
45	Thr Leu Glu Ser Ser Ala Gly Ala Glu Leu Ser Phe Ile Leu Pro Arg 785	790	795
	Glu Ser Thr His Arg Phe Glu Gly Leu Phe Ala Lys Leu Glu Lys Lys 805	810	815
50	Gln Lys Glu Leu Gly Ile Ala Ser Phe Gly Ala Ser Ile Thr Thr Met		

	820	825	830
5	Glu Glu Val Phe Leu Arg Val Gly Lys Leu Val Asp Ser Ser Met Asp 835	840	845
10	Ile Gln Ala Ile Gln Leu Pro Ala Leu Gln Tyr Gln His Glu Arg Arg 850	855	860
15	Ala Ser Asp Trp Ala Val Asp Ser Asn Leu Cys Gly Ala Met Asp Pro 865	870	875
20	Ser Asp Gly Ile Gly Ala Leu Ile Glu Glu Glu Arg Thr Ala Val Lys 885	890	895
25	Leu Asn Thr Gly Leu Ala Leu His Cys Gln Gln Phe Trp Ala Met Phe 900	905	910
30	Leu Lys Lys Ala Ala Tyr Ser Trp Arg Glu Trp Lys Met Val Ala Ala 915	920	925
35	Gln Val Leu Val Pro Leu Thr Cys Val Thr Leu Ala Leu Ala Ile 930	935	940
40	Asn Tyr Ser Ser Glu Leu Phe Asp Asp Pro Met Leu Arg Leu Thr Leu 945	950	955
45	Gly Glu Tyr Gly Arg Thr Val Val Pro Phe Ser Val Pro Gly Thr Ser 965	970	975
50	Gln Leu Gly Gln Gln Leu Ser Glu His Leu Lys Asp Ala Leu Gln Ala 980	985	990
55	Glu Gly Gln Glu Pro Arg Glu Val Leu Gly Asp Leu Glu Glu Phe Leu 995	1000	1005
60	Ile Phe Arg Ala Ser Val Glu Gly Gly Phe Asn Glu Arg Cys Leu 1010	1015	1020
65	Val Ala Ala Ser Phe Arg Asp Val Gly Glu Arg Thr Val Val Asn Ala 1025	1030	1035
70	Leu Phe Asn Asn Gln Ala Tyr His Ser Pro Ala Thr Ala Leu Ala Val 1045	1050	1055
75	Val Asp Asn Leu Leu Phe Lys Leu Leu Cys Gly Pro His Ala Ser Ile 1060	1065	1070
80	Val Val Ser Asn Phe Pro Gln Pro Arg Ser Ala Leu Gln Ala Ala Lys		

EP 1 217 066 A1

5	1075	1080	1085
	Asp Gln Phe Asn Glu Gly Arg Lys Gly Phe Asp Ile Ala Leu Asn Leu		
	1090	1095	1100
	Leu Phe Ala Met Ala Phe Leu Ala Ser Thr Phe Ser Ile Leu Ala Val		
10	1105	1110	1115
	Ser Glu Arg Ala Val Gln Ala Lys His Val Gln Phe Val Ser Gly Val		
	1125	1130	1135
15	His Val Ala Ser Phe Trp Leu Ser Ala Leu Leu Trp Asp Leu Ile Ser		
	1140	1145	1150
	Phe Leu Ile Pro Ser Leu Leu Leu Val Val Phe Lys Ala Phe Asp		
20	1155	1160	1165
	Val Arg Ala Phe Thr Arg Asp Gly His Met Ala Asp Thr Leu Leu Leu		
	1170	1175	1180
25	Leu Leu Leu Tyr Gly Trp Ala Ile Ile Pro Leu Met Tyr Leu Met Asn		
	1185	1190	1195
	Phe Phe Phe Leu Gly Ala Ala Thr Ala Tyr Thr Arg Leu Thr Ile Phe		
30	1205	1210	1215
	Asn Ile Leu Ser Gly Ile Ala Thr Phe Leu Met Val Thr Ile Met Arg		
	1220	1225	1230
35	Ile Pro Ala Val Lys Leu Glu Glu Leu Ser Lys Thr Leu Asp His Val		
	1235	1240	1245
	Phe Leu Val Leu Pro Asn His Cys Leu Gly Met Ala Val Ser Ser Phe		
40	1250	1255	1260
	Tyr Glu Asn Tyr Glu Thr Arg Arg Tyr Cys Thr Ser Ser Glu Val Ala		
	1265	1270	1275
	Ala His Tyr Cys Lys Lys Tyr Asn Ile Gln Tyr Gln Glu Asn Phe Tyr		
45	1285	1290	1295
	Ala Trp Ser Ala Pro Gly Val Gly Arg Phe Val Ala Ser Met Ala Ala		
50	1300	1305	1310
	Ser Gly Cys Ala Tyr Leu Ile Leu Leu Phe Leu Ile Glu Thr Asn Leu		
	1315	1320	1325
55	Leu Gln Arg Leu Arg Gly Ile Leu Cys Ala Leu Arg Arg Arg Arg Thr		

EP 1 217 066 A1

	1330	1335	1340
5	Leu Thr Glu Leu Tyr Thr Arg Met Pro Val Leu Pro Glu Asp Gln Asp		
	1345	1350	1355
	Val Ala Asp Glu Arg Thr Arg Ile Leu Ala Pro Ser Pro Asp Ser Leu		
10	1365	1370	1375
	Leu His Thr Pro Leu Ile Ile Lys Glu Leu Ser Lys Val Tyr Glu Gln		
	1380	1385	1390
15	Arg Val Pro Leu Leu Ala Val Asp Arg Leu Ser Leu Ala Val Gln Lys		
	1395	1400	1405
	Gly Glu Cys Phe Gly Leu Leu Gly Phe Asn Gly Ala Gly Lys Thr Thr		
20	1410	1415	1420
	Thr Phe Lys Met Leu Thr Gly Glu Glu Ser Leu Thr Ser Gly Asp Ala		
	1425	1430	1435
	Phe Val Gly Gly His Arg Ile Ser Ser Asp Val Gly Lys Val Arg Gln		
25	1445	1450	1455
	Arg Ile Gly Tyr Cys Pro Gln Phe Asp Ala Leu Leu Asp His Met Thr		
30	1460	1465	1470
	Gly Arg Glu Met Leu Val Met Tyr Ala Arg Leu Arg Gly Ile Pro Glu		
	1475	1480	1485
35	Arg His Ile Gly Ala Cys Val Glu Asn Thr Leu Arg Gly Leu Leu Leu		
	1490	1495	1500
	Glu Pro His Ala Asn Lys Leu Val Arg Thr Tyr Ser Gly Gly Asn Lys		
40	1505	1510	1515
	Arg Lys Leu Ser Thr Gly Ile Ala Leu Ile Gly Glu Pro Ala Val Ile		
	1525	1530	1535
45	Phe Leu Asp Glu Pro Ser Thr Gly Met Asp Pro Val Ala Arg Arg Leu		
	1540	1545	1550
	Leu Trp Asp Thr Val Ala Arg Ala Arg Glu Ser Gly Lys Ala Ile Ile		
50	1555	1560	1565
	Ile Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu		
	1570	1575	1580
55	Ala Ile Met Val Gln Gly Gln Phe Lys Cys Leu Gly Ser Pro Gln His		

EP 1 217 066 A1

1585	1590	1595	1600
Leu Lys Ser Lys Phe Gly Ser Gly Tyr Ser Leu Arg Ala Lys Val Gln			
5 1605	1610	1615	
Ser Glu Gly Gln Gln Glu Ala Leu Glu Glu Phe Lys Ala Phe Val Asp			
10 1620	1625	1630	
Leu Thr Phe Pro Gly Ser Val Leu Glu Asp Glu His Gln Gly Met Val			
1635	1640	1645	
His Tyr His Leu Pro Gly Arg Asp Leu Ser Trp Ala Lys Val Phe Gly			
15 1650	1655	1660	
Ile Leu Glu Lys Ala Lys Glu Lys Tyr Gly Val Asp Asp Tyr Ser Val			
20 1665	1670	1675	1680
Ser Gln Ile Ser Leu Glu Gln Val Phe Leu Ser Phe Ala His Leu Gln			
1685	1690	1695	
Pro Pro Thr Ala Glu Glu Gly Arg			
25 1700			
30 <210> 47			
<211> 2273			
<212> PRT			
<213> Homo sapiens			
35 <400> 47			
Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr			
1	5	10	15
40 Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro	20	25	30
Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu			
45 35	40	45	
Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala			
50 50	55	60	
55 Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro	65	70	75
Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn			
55 85	90	95	

EP 1 217 066 A1

Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu
 100 105 110

5 Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu
 115 120 125

10 Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu
 130 135 140

15 Arg Ile Ala Gly Arg Gly Ile Arg Asp Ile Leu Lys Asp Glu
 145 150 155 160

20 Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser
 165 170 175

25 Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala
 180 185 190

His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala
 195 200 205

30 Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr
 210 215 220

35 Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile
 225 230 235 240

Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val
 245 250 255

40 Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser
 260 265 270

Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile
 275 280 285

45 His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met
 290 295 300

Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser
 305 310 315 320

50 Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Ser Arg Val Leu Ser
 325 330 335

55 Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp
 340 345 350

EP 1 217 066 A1

Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser
355 360 365

5 Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys
370 375 380

10 Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr
385 390 395 400

15 Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser
405 410 415

20 Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu
420 425 430

25 Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met
435 440 445

Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu
25 450 455 460

465 Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn
470 475 480

30 Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn
485 490 495

35 Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu
500 505 510

Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr
515 520 525

40 Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu
530 535 540

45 Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr
545 550 555 560

50 Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp
565 570 575

Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly
580 585 590

55 Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe
595 600 605

EP 1 217 066 A1

Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val
610 615 620

5 Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro
625 630 635 640

10 Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro
645 650 655

Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys
660 665 670

15 Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn
675 680 685

20 Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser
690 695 700

Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met
705 710 715 720

25 His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe
725 730 735

30 Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser
740 745 750

35 Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile
755 760 765

Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp
770 775 780

40 Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val
785 790 795 800

45 Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly
805 810 815

Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp
820 825 830

50 Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala
835 840 845

55 Cys Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp
850 855 860

EP 1 217 066 A1

Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp
 865 870 875 880
 5 Leu Ser Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys
 885 890 895
 Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly
 10 900 905 910
 Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly
 915 920 925
 15 Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro
 930 935 940
 Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala
 20 945 950 955 960
 Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu
 25 965 970 975
 Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg
 980 985 990
 Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys
 30 995 1000 1005
 Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met
 35 1010 1015 1020
 Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Ala Gln Leu
 1025 1030 1035 1040
 40 Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn
 1045 1050 1055
 Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val
 45 1060 1065 1070
 Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro
 1075 1080 1085
 50 Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu
 1090 1095 1100
 Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Pro Thr His His Met
 55 1105 1110 1115 1120

EP 1217066 A1

Asp Glu Ala Asp His Gln Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly
1125 1130 1135

5 Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly
1140 1145 1150

10 Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser
1155 1160 1165

Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe
1170 1175 1180

15 Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln Val
1185 1190 1195 1200

20 Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val Leu His His Val
1205 1210 1215

Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu
1220 1225 1230

25 Leu Pro Asn Lys Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe Arg
1235 1240 1245

30 Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly Ile
1250 1255 1260

Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp Ser
1265 1270 1275 1280

35 Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln Lys Arg Glu Asn
1285 1290 1295

40 Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu Lys Ala Gly Gln
1300 1305 1310

45 Thr Pro Gln Asp Ser Asn Val Cys Ser Pro Gly Ala Pro Ala Ala His
1315 1320 1325

Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro Gly Pro Gln Leu
1330 1335 1340

50 Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln Ala Leu Leu Val
1345 1350 1355 1360

55 Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp Phe Leu Ala Gln
1365 1370 1375

EP 1 217 066 A1

Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu Met Leu Ser Ile
1380 1385 1390

5 Val Ile Leu Pro Phe Gly Glu Tyr Pro Ala Leu Thr Leu His Pro Trp
1395 1400 1405

Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp Glu Pro Gly Ser
10 1410 1415 1420

Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn Lys Pro Gly Phe
1425 1430 1435 1440

15 Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu Tyr Pro Cys Gly
1445 1450 1455

Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser Pro Asn Ile Thr Gln
20 1460 1465 1470

Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn Pro Ser Pro Ser Cys
25 1475 1480 1485

Arg Cys Ser Thr Arg Glu Lys Leu Thr Met Leu Pro Glu Cys Pro Glu
1490 1495 1500

Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg Ser Thr Glu
30 1505 1510 1515 1520

Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe Leu Val Lys
35 1525 1530 1535

Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys Phe Trp Val
1540 1545 1550

40 Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys Leu Pro Val
1555 1560 1565

Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu Ser Asp Leu Gly
45 1570 1575 1580

Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys
1585 1590 1595 1600

50 Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile Lys
1605 1610 1615

55 Val Trp Phe Asn Asn Lys Gly Trp His Ala Leu Val Ser Phe Leu Asn
1620 1625 1630

EP 1217 066 A1

Val Ala His Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys Asp Arg Ser
 1635 1640 1645
 5 Pro Glu Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu Asn Leu Thr
 1650 1655 1660
 Lys Glu Gln Leu Ser Glu Ile Thr Val Leu Thr Thr Ser Val Asp Ala
 10 1665 1670 1675 1680
 Val Val Ala Ile Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala Ser
 1685 1690 1695
 15 Phe Val Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His Leu
 1700 1705 1710
 Gln Phe Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe
 20 1715 1720 1725
 Leu Trp Asp Ile Met Asn Tyr Ser Val Ser Ala Gly Leu Val Val Gly
 1730 1735 1740
 25 Ile Phe Ile Gly Phe Gln Lys Lys Ala Tyr Thr Ser Pro Glu Asn Leu
 1745 1750 1755 1760
 Pro Ala Leu Val Ala Leu Leu Leu Tyr Gly Trp Ala Val Ile Pro
 30 1765 1770 1775
 Met Met Tyr Pro Ala Ser Phe Leu Phe Asp Val Pro Ser Thr Ala Tyr
 35 1780 1785 1790
 Val Ala Leu Ser Cys Ala Asn Leu Phe Ile Gly Ile Asn Ser Ser Ala
 1795 1800 1805
 40 Ile Thr Phe Ile Leu Glu Leu Phe Asp Asn Asn Arg Thr Leu Leu Arg
 1810 1815 1820
 Phe Asn Ala Val Leu Arg Lys Leu Leu Ile Val Phe Pro His Phe Cys
 45 1825 1830 1835 1840
 Leu Gly Arg Gly Leu Ile Asp Leu Ala Leu Ser Gln Ala Val Thr Asp
 1845 1850 1855
 50 Val Tyr Ala Arg Phe Gly Glu Glu His Ser Ala Asn Pro Phe His Trp
 1860 1865 1870
 Asp Leu Ile Gly Lys Asn Leu Phe Ala Met Val Val Glu Gly Val Val
 55 1875 1880 1885

EP 1 217 066 A1

Tyr Phe Leu Leu Thr Leu Leu Val Gln Arg His Phe Phe Leu Ser Gln
1890 1895 1900

5 Trp Ile Ala Glu Pro Thr Lys Glu Pro Ile Val Asp Glu Asp Asp Asp
1905 1910 1915 1920

10 Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly Gly Asn Lys Thr Asp
1925 1930 1935

Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr Leu Gly Thr Ser Ser
1940 1945 1950

15 Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg Pro Gly Glu Cys Phe
1955 1960 1965

20 Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Thr Phe Lys Met
1970 1975 1980

Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp Ala Thr Val Ala Gly
25 1985 1990 1995 2000

Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His Gln Asn Met Gly Tyr
2005 2010 2015

30 Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu Thr Gly Arg Glu His
2020 2025 2030

Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro Ala Glu Glu Ile Glu
35 2035 2040 2045

Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly Leu Thr Val Tyr Ala
2050 2055 2060

40 Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser
2065 2070 2075 2080

45 Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val Leu Asp Glu
2085 2090 2095

Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met Leu Trp Asn Val
50 2100 2105 2110

Ile Val Ser Ile Ile Arg Lys Gly Arg Ala Val Val Leu Thr Ser His
2115 2120 2125

55 Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met Val
2130 2135 2140

EP 1 217 066 A1

Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser Lys
2145 2150 2155 2160

5 Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys Asp
2165 2170 2175

10 Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly Asn
2180 2185 2190

Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln Phe
2195 2200 2205

15 Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu Ser
2210 2215 2220

20 His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr
2225 2230 2235 2240

25 Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser His
2245 2250 2255

Asp Leu Pro Leu His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala Gln
2260 2265 2270

30 Asp

35 <210> 48
<211> 2146
<212> PRT
<213> Homo sapiens

40 <400> 48
Met Ala Phe Trp Thr Gln Leu Met Leu Leu Leu Trp Lys Asn Phe Met
1 5 10 15

45 Tyr Arg Arg Arg Gln Pro Val Gln Leu Leu Val Glu Leu Leu Trp Pro
20 25 30

50 Leu Phe Leu Phe Phe Ile Leu Val Ala Val Arg His Ser His Pro Pro
35 40 45

55 Leu Glu His His Glu Cys His Phe Pro Asn Lys Pro Leu Pro Ser Ala
50 55 60

EP 1 217 066 A1

	Gly Thr Val Pro Trp Leu Gln Gly Leu Ile Cys Asn Val Asn Asn Thr		
5	65	70	75
	Cys Phe Pro Gln Leu Thr Pro Gly Glu Glu Pro Gly Arg Leu Ser Asn		
	85	90	95
10	Phe Asn Asp Ser Leu Val Ser Arg Leu Leu Ala Asp Ala Arg Thr Val		
	100	105	110
15	Leu Gly Gly Ala Ser Ala His Arg Thr Leu Ala Gly Leu Gly Lys Leu		
	115	120	125
	Ile Ala Thr Leu Arg Ala Ala Arg Ser Thr Ala Gln Pro Gln Pro Thr		
	130	135	140
20	Lys Gln Ser Pro Leu Glu Pro Pro Met Leu Asp Val Ala Glu Leu Leu		
	145	150	155
	160		
25	Thr Ser Leu Leu Arg Thr Glu Ser Leu Gly Leu Ala Leu Gly Gln Ala		
	165	170	175
	Gln Glu Pro Leu His Ser Leu Leu Glu Ala Ala Glu Asp Leu Ala Gln		
	180	185	190
30	Glu Leu Leu Ala Leu Arg Ser Leu Val Glu Leu Arg Ala Leu Leu Gln		
	195	200	205
35	Arg Pro Arg Gly Thr Ser Gly Pro Leu Glu Leu Leu Ser Glu Ala Leu		
	210	215	220
	Cys Ser Val Arg Gly Pro Ser Ser Thr Val Gly Pro Ser Leu Asn Trp		
	225	230	235
	240		
40	Tyr Glu Ala Ser Asp Leu Met Glu Leu Val Gly Gln Glu Pro Glu Ser		
	245	250	255
45	Ala Leu Pro Asp Ser Ser Leu Ser Pro Ala Cys Ser Glu Leu Ile Gly		
	260	265	270
	Ala Leu Asp Ser His Pro Leu Ser Arg Leu Leu Trp Arg Arg Leu Lys		
	275	280	285
50	Pro Leu Ile Leu Gly Lys Leu Leu Phe Ala Pro Asp Thr Pro Phe Thr		
	290	295	300
55	Arg Lys Leu Met Ala Gln Val Asn Arg Thr Phe Glu Glu Leu Thr Leu		
	305	310	315
	320		

Leu Arg Asp Val Arg Glu Val Trp Glu Met Leu Gly Pro Arg Ile Phe
 325 330 335
 5 Thr Phe Met Asn Asp Ser Ser Asn Val Ala Met Leu Gln Arg Leu Leu
 340 345 350
 10 Gln Met Gln Asp Glu Gly Arg Arg Gln Pro Arg Pro Gly Gly Arg Asp
 355 360 365
 His Met Glu Ala Leu Arg Ser Phe Leu Asp Pro Gly Ser Gly Gly Tyr
 370 375 380
 15 Ser Trp Gln Asp Ala His Ala Asp Val Gly His Leu Val Gly Thr Leu
 385 390 395 400
 20 Gly Arg Val Thr Glu Cys Leu Ser Leu Asp Lys Leu Glu Ala Ala Pro
 405 410 415
 25 Ser Glu Ala Ala Leu Val Ser Arg Ala Leu Gln Leu Leu Ala Glu His
 420 425 430
 Arg Phe Trp Ala Gly Val Val Phe Leu Gly Pro Glu Asp Ser Ser Asp
 435 440 445
 30 Pro Thr Glu His Pro Thr Pro Asp Leu Gly Pro Gly His Val Arg Ile
 450 455 460
 35 Lys Ile Arg Met Asp Ile Asp Val Val Thr Arg Thr Asn Lys Ile Arg
 465 470 475 480
 Asp Arg Phe Trp Asp Pro Gly Pro Ala Ala Asp Pro Leu Thr Asp Leu
 485 490 495
 40 Arg Tyr Val Trp Gly Gly Phe Val Tyr Leu Gln Asp Leu Val Glu Arg
 500 505 510
 45 Ala Ala Val Arg Val Leu Ser Gly Ala Asn Pro Arg Ala Gly Leu Tyr
 515 520 525
 Leu Gln Gln Met Pro Tyr Pro Cys Tyr Val Asp Asp Val Phe Leu Arg
 530 535 540
 50 Val Leu Ser Arg Ser Leu Pro Leu Phe Leu Thr Leu Ala Trp Ile Tyr
 545 550 555 560
 55 Ser Val Thr Leu Thr Val Lys Ala Val Val Arg Glu Lys Glu Thr Arg
 565 570 575

EP 1 217 066 A1

Leu Arg Asp Thr Met Arg Ala Met Gly Leu Ser Arg Ala Val Leu Trp
580 585 590

5 Leu Gly Trp Phe Leu Ser Cys Leu Gly Pro Phe Leu Leu Ser Ala Ala
595 600 605

10 Leu Leu Val Leu Val Leu Lys Leu Gly Asp Ile Leu Pro Tyr Ser His
610 615 620

15 Pro Gly Val Val Phe Leu Phe Leu Ala Ala Phe Ala Val Ala Thr Val
625 630 635 640

15 Thr Gln Ser Phe Leu Leu Ser Ala Phe Phe Ser Arg Ala Asn Leu Ala
645 650 655

20 Ala Ala Cys Gly Gly Leu Ala Tyr Phe Ser Leu Tyr Leu Pro Tyr Val
660 665 670

25 Leu Cys Val Ala Trp Arg Asp Arg Leu Pro Ala Gly Gly Arg Val Ala
675 680 685

25 Ala Ser Leu Leu Ser Pro Val Ala Phe Gly Phe Gly Cys Glu Ser Leu
690 695 700

30 Ala Leu Leu Glu Glu Gln Gly Glu Gly Ala Gln Trp His Asn Val Gly
705 710 715 720

35 Thr Arg Pro Thr Ala Asp Val Phe Ser Leu Ala Gln Val Ser Gly Leu
725 730 735

Leu Leu Leu Asp Ala Ala Leu Tyr Gly Leu Ala Thr Trp Tyr Leu Glu
740 745 750

40 Ala Val Cys Pro Gly Gln Tyr Gly Ile Pro Glu Pro Trp Asn Phe Pro
755 760 765

45 Phe Arg Arg Ser Tyr Trp Cys Gly Pro Arg Pro Pro Lys Ser Pro Ala
770 775 780

Pro Cys Pro Thr Pro Leu Asp Pro Lys Val Leu Val Glu Glu Ala Pro
785 790 795 800

50 Pro Gly Leu Ser Pro Gly Val Ser Val Arg Ser Leu Glu Lys Arg Phe
805 810 815

55 Pro Gly Ser Pro Gln Pro Ala Leu Arg Gly Leu Ser Leu Asp Phe Tyr
820 825 830

Gln Gly His Ile Thr Ala Phe Leu Gly His Asn Gly Ala Gly Lys Thr
 835 840 845
 5

Thr Thr Leu Ser Ile Leu Ser Gly Leu Phe Pro Pro Ser Gly Gly Ser
 850 855 860

10 Ala Phe Ile Leu Gly His Asp Val Arg Ser Ser Met Ala Ala Ile Arg
 865 870 875 880

Pro His Leu Gly Val Cys Pro Gln Tyr Asn Val Leu Phe Asp Met Leu
 15 885 890 895

Thr Val Asp Glu His Val Trp Phe Tyr Gly Arg Leu Lys Gly Leu Ser
 900 905 910

20 Ala Ala Val Val Gly Pro Glu Gln Asp Arg Leu Leu Gln Asp Val Gly
 915 920 925

25 Leu Val Ser Lys Gln Ser Val Gln Thr Arg His Leu Ser Gly Gly Met
 930 935 940

Gln Arg Lys Leu Ser Val Ala Ile Ala Phe Val Gly Gly Ser Gln Val
 945 950 955 960

30 Val Ile Leu Asp Glu Pro Thr Ala Gly Val Asp Pro Ala Ser Arg Arg
 965 970 975

35 Gly Ile Trp Glu Leu Leu Lys Tyr Arg Glu Gly Arg Thr Leu Ile
 980 985 990

Leu Ser Thr His His Leu Asp Glu Ala Glu Leu Leu Gly Asp Arg Val
 995 1000 1005

40 Ala Val Val Ala Gly Gly Arg Leu Cys Cys Cys Gly Ser Pro Leu Phe
 1010 1015 1020

45 Leu Arg Arg His Leu Gly Ser Gly Tyr Tyr Leu Thr Leu Val Lys Ala
 1025 1030 1035 1040

Arg Leu Pro Leu Thr Thr Asn Glu Lys Ala Asp Thr Asp Met Glu Gly
 1045 1050 1055

50 Ser Val Asp Thr Arg Gln Glu Lys Lys Asn Gly Ser Gln Gly Ser Arg
 1060 1065 1070

55 Val Gly Thr Pro Gln Leu Leu Ala Leu Val Gln His Trp Val Pro Gly
 1075 1080 1085

EP 1 217 066 A1

Ala Arg Leu Val Glu Glu Leu Pro His Glu Leu Val Leu Val Leu Pro
1090 1095 1100

5 Tyr Thr Gly Ala His Asp Gly Ser Phe Ala Thr Leu Phe Arg Glu Leu
1105 1110 1115 1120

10 Asp Thr Arg Leu Ala Glu Leu Arg Leu Thr Gly Tyr Gly Ile Ser Asp
1125 1130 1135

15 Thr Ser Leu Glu Glu Ile Phe Leu Lys Val Val Glu Glu Cys Ala Ala
1140 1145 1150

19 Asp Thr Asp Met Glu Asp Gly Ser Cys Gly Gln His Leu Cys Thr Gly
1155 1160 1165

20 Ile Ala Gly Leu Asp Val Thr Leu Arg Leu Lys Met Pro Pro Gln Glu
1170 1175 1180

25 Thr Ala Leu Glu Asn Gly Glu Pro Ala Gly Ser Ala Pro Glu Thr Asp
1185 1190 1195 1200

29 Gln Gly Ser Gly Pro Asp Ala Val Gly Arg Val Gln Gly Trp Ala Leu
1205 1210 1215

30 Thr Arg Gln Gln Leu Gln Ala Leu Leu Leu Lys Arg Phe Leu Leu Ala
1220 1225 1230

35 Arg Arg Ser Arg Arg Gly Leu Phe Ala Gln Ile Val Leu Pro Ala Leu
1235 1240 1245

40 Phe Val Gly Leu Ala Leu Val Phe Ser Leu Ile Val Pro Pro Phe Gly
1250 1255 1260

45 His Tyr Pro Ala Leu Arg Leu Ser Pro Thr Met Tyr Gly Ala Gln Val
1265 1270 1275 1280

50 Ser Phe Phe Ser Glu Asp Ala Pro Gly Asp Pro Gly Arg Ala Arg Leu
1285 1290 1295

55 Leu Glu Ala Leu Leu Gln Glu Ala Gly Leu Glu Glu Pro Pro Val Gln
1300 1305 1310

His Ser Ser His Arg Phe Ser Ala Pro Glu Val Pro Ala Glu Val Ala
1315 1320 1325

Lys Val Leu Ala Ser Gly Asn Trp Thr Pro Glu Ser Pro Ser Pro Ala
1330 1335 1340

EP 1 217 066 A1

Cys Gln Cys Ser Gln Pro Gly Ala Arg Arg Leu Leu Pro Asp Cys Pro
1345 1350 1355 1360

5 Ala Ala Ala Gly Gly Pro Pro Pro Pro Gln Ala Val Thr Gly Ser Gly
1365 1370 1375

10 Glu Val Val Gln Asn Leu Thr Gly Arg Asn Leu Ser Asp Phe Leu Val
1380 1385 1390

Lys Thr Tyr Pro Arg Leu Val Arg Gln Gly Leu Lys Thr Lys Lys Trp
1395 1400 1405

15 Val Asn Glu Val Arg Tyr Gly Gly Phe Ser Leu Gly Gly Arg Asp Pro
1410 1415 1420

20 Gly Leu Pro Ser Gly Gln Glu Leu Gly Arg Ser Val Glu Glu Leu Trp
1425 1430 1435 1440

Ala Leu Leu Ser Pro Leu Pro Gly Gly Ala Leu Asp Arg Val Leu Lys
25 1445 1450 1455

Asn Leu Thr Ala Trp Ala His Ser Leu Asp Ala Gln Asp Ser Leu Lys
1460 1465 1470

30 Ile Trp Phe Asn Asn Lys Gly Trp His Ser Met Val Ala Phe Val Asn
1475 1480 1485

Arg Ala Ser Asn Ala Ile Leu Arg Ala His Leu Pro Pro Gly Arg Ala
35 1490 1495 1500

Arg His Ala His Ser Ile Thr Thr Leu Asn His Pro Leu Asn Leu Thr
1505 1510 1515 1520

40 Lys Glu Gln Leu Phe Glu Ala Ala Leu Met Ala Ser Ser Val Asp Val
1525 1530 1535

Leu Val Ser Ile Cys Val Val Phe Ala Met Ser Phe Val Pro Ala Ser
45 1540 1545 1550

Phe Thr Leu Val Leu Ile Glu Glu Arg Val Thr Arg Ala Lys His Leu
1555 1560 1565

50 Gln Leu Met Gly Gly Leu Ser Pro Thr Leu Tyr Trp Leu Gly Asn Phe
1570 1575 1580

Leu Trp Asp Met Cys Asn Tyr Leu Val Pro Ala Cys Ile Val Val Leu
55 1585 1590 1595 1600

EP 1 217 066 A1

Ile Phe Leu Ala Phe Gln Gln Arg Ala Tyr Val Ala Pro Ala Asn Leu
 1605 1610 1615

5 Pro Ala Leu Leu Leu Leu Leu Leu Tyr Gly Trp Ser Ile Thr Pro
 1620 1625 1630

10 Leu Met Tyr Pro Ala Ser Phe Phe Phe Ser Val Pro Ser Thr Ala Tyr
 1635 1640 1645

15 Val Val Leu Thr Cys Ile Asn Leu Phe Ile Gly Ile Asn Gly Ser Met
 1650 1655 1660

Ala Thr Phe Val Leu Glu Leu Phe Ser Asp Gln Lys Leu Gln Glu Val
 1665 1670 1675 1680

20 Ser Arg Ile Leu Lys Gln Val Phe Leu Ile Phe Pro His Phe Cys Leu
 1685 1690 1695

Gly Arg Gly Leu Ile Asp Met Val Arg Asn Gln Ala Met Ala Asp Ala
 25 1700 1705 1710

Phe Glu Arg Leu Gly Asp Arg Gln Phe Gln Ser Pro Leu Arg Trp Glu
 1715 1720 1725

30 Val Val Gly Lys Asn Leu Leu Ala Met Val Ile Gln Gly Pro Leu Phe
 1730 1735 1740

Leu Leu Phe Thr Leu Leu Leu Gln His Arg Ser Gln Leu Leu Pro Gln
 35 1745 1750 1755 1760

Pro Arg Val Arg Ser Leu Pro Leu Leu Gly Glu Glu Asp Glu Asp Val
 1765 1770 1775

40 Ala Arg Glu Arg Glu Arg Val Val Gln Gly Ala Thr Gln Gly Asp Val
 1780 1785 1790

Leu Val Leu Arg Asn Leu Thr Lys Val Tyr Arg Gly Gln Arg Met Pro
 45 1795 1800 1805

Ala Val Asp Arg Leu Cys Leu Gly Ile Pro Pro Gly Glu Cys Phe Gly
 1810 1815 1820

50 Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Ser Thr Phe Arg Met Val
 1825 1830 1835 1840

Thr Gly Asp Thr Leu Ala Ser Arg Gly Glu Ala Val Leu Ala Gly His
 55 1845 1850 1855

EP 1 217 066 A1

	Ser Val Ala Arg Glu Pro Ser Ala Ala His Leu Ser Met Gly Tyr Cys			
	1860	1865	1870	
5	Pro Gln Ser Asp Ala Ile Phe Glu Leu Leu Thr Gly Arg Glu His Leu			
	1875	1880	1885	
10	Glu Leu Leu Ala Arg Leu Arg Gly Val Pro Glu Ala Gln Val Ala Gln			
	1890	1895	1900	
15	Thr Ala Gly Ser Gly Leu Ala Arg Leu Gly Leu Ser Trp Tyr Ala Asp			
	1905	1910	1915	1920
	Arg Pro Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ala Thr			
	1925	1930	1935	
20	Ala Leu Ala Leu Val Gly Asp Pro Ala Val Val Phe Leu Asp Glu Pro			
	1940	1945	1950	
25	Thr Thr Gly Met Asp Pro Ser Ala Arg Arg Phe Leu Trp Asn Ser Leu			
	1955	1960	1965	
	Leu Ala Val Val Arg Glu Gly Arg Ser Val Met Leu Thr Ser His Ser			
	1970	1975	1980	
30	Met Glu Glu Cys Glu Ala Leu Cys Ser Arg Leu Ala Ile Met Val Asn			
	1985	1990	1995	2000
35	Gly Arg Phe Arg Cys Leu Gly Ser Pro Gln His Leu Lys Gly Arg Phe			
	2005	2010	2015	
	Ala Ala Gly His Thr Leu Thr Leu Arg Val Pro Ala Ala Arg Ser Gln			
	2020	2025	2030	
40	Pro Ala Ala Ala Phe Val Ala Ala Glu Phe Pro Gly Ser Glu Leu Arg			
	2035	2040	2045	
45	Glu Ala His Gly Gly Arg Leu Arg Phe Gln Leu Pro Pro Gly Gly Arg			
	2050	2055	2060	
	Cys Ala Leu Ala Arg Val Phe Gly Glu Leu Ala Val His Gly Ala Glu			
	2065	2070	2075	2080
50	His Gly Val Glu Asp Phe Ser Val Ser Gln Thr Met Leu Glu Glu Val			
	2085	2090	2095	
55	Phe Leu Tyr Phe Ser Lys Asp Gln Gly Lys Asp Glu Asp Thr Glu Glu			
	2100	2105	2110	

EP 1 217 066 A1

Gln Lys Glu Ala Gly Val Gly Val Asp Pro Ala Pro Gly Leu Gln His
2115 2120 2125

5 Pro Lys Arg Val Ser Gln Phe Leu Asp Asp Pro Ser Thr Ala Glu Thr
2130 2135 2140

10 Val Leu
2145

15 <210> 49
<211> 1581
<212> PRT
<213> Homo sapiens

20 <400> 49
Met Arg Lys Arg Lys Ile Ser Val Cys Gln Gln Thr Trp Ala Leu Leu
1 5 10 15

25 Cys Lys Asn Phe Leu Lys Lys Trp Arg Met Lys Arg Glu Ser Leu Met
20 25 30

30 Glu Trp Leu Asn Ser Leu Leu Leu Leu Cys Leu Tyr Ile Tyr Pro
35 40 45

His Ser His Gln Val Asn Asp Phe Ser Ser Leu Leu Thr Met Asp Leu
50 55 60

35 Gly Arg Val Asp Thr Phe Asn Glu Ser Arg Phe Ser Val Val Tyr Thr
65 70 75 80

40 Pro Val Thr Asn Thr Thr Gln Gln Ile Met Asn Lys Val Ala Ser Thr
85 90 95

Pro Phe Leu Ala Gly Lys Glu Val Leu Gly Leu Pro Asp Glu Glu Ser
100 105 110

45 Ile Lys Glu Phe Thr Ala Asn Tyr Pro Glu Glu Ile Val Arg Val Thr
115 120 125

50 Phe Thr Asn Thr Tyr Ser Tyr His Leu Lys Phe Leu Leu Gly His Gly
130 135 140

Met Pro Ala Lys Lys Glu His Lys Asp His Thr Ala His Cys Tyr Glu
145 150 155 160

55 Thr Asn Glu Asp Val Tyr Cys Glu Val Ser Val Phe Trp Lys Glu Gly

EP 1 217 066 A1

	165	170	175
5	Phe Val Ala Leu Gln Ala Ala Ile Asn Ala Ala Ile Ile Glu Ile Thr 180	185	190
10	Thr Asn His Ser Val Met Glu Glu Leu Met Ser Val Thr Gly Lys Asn 195	200	205
15	Met Lys Met His Ser Phe Ile Gly Gln Ser Gly Val Ile Thr Asp Leu 210	215	220
20	Tyr Leu Phe Ser Cys Ile Ile Ser Phe Ser Ser Phe Ile Tyr Tyr Ala 225	230	235
25	Ser Val Asn Val Thr Arg Glu Arg Lys Arg Met Lys Ala Leu Met Thr 245	250	255
30	Met Met Gly Leu Arg Asp Ser Ala Phe Trp Leu Ser Trp Gly Leu Leu 260	265	270
35	Tyr Ala Gly Phe Ile Phe Ile Met Ala Leu Phe Leu Ala Leu Val Ile 275	280	285
40	Arg Ser Thr Gln Phe Ile Ile Leu Ser Gly Phe Met Val Val Phe Ser 290	295	300
45	Leu Phe Leu Leu Tyr Gly Leu Ser Leu Val Ala Leu Ala Phe Leu Met 305	310	315
50	Ser Ile Leu Val Lys Lys Ser Phe Leu Thr Gly Leu Val Val Phe Leu 325	330	335
55	Leu Thr Val Phe Trp Gly Cys Leu Gly Phe Thr Ser Leu Tyr Arg His 340	345	350
	Leu Pro Ala Ser Leu Glu Trp Ile Leu Ser Leu Leu Ser Pro Phe Ala 355	360	365
	Phe Met Leu Gly Met Ala Gln Leu Leu His Leu Asp Tyr Asp Leu Asn 370	375	380
	Ser Asn Ala Phe Pro His Pro Ser Asp Gly Ser Asn Leu Ile Val Ala 385	390	395
	Thr Asn Phe Met Leu Ala Phe Asp Thr Cys Leu Tyr Leu Ala Leu Ala 405	410	415
	Ile Tyr Phe Glu Lys Ile Leu Pro Asn Glu Tyr Gly His Arg Arg Pro		

EP 1 217 066 A1

	420	425	430
5	Pro Leu Phe Phe Leu Lys Ser Ser Phe Trp Ser Gln Thr Gln Lys Thr		
	435	440	445
	Asp His Val Ala Leu Glu Asp Glu Met Asp Ala Asp Pro Ser Phe His		
10	450	455	460
	Asp Ser Phe Glu Gln Ala Pro Pro Glu Phe Gln Gly Lys Glu Ala Ile		
	465	470	475
15	Arg Ile Arg Asn Val Thr Lys Glu Tyr Lys Gly Lys Pro Asp Lys Ile		
	485	490	495
20	Glu Ala Leu Lys Asp Leu Val Phe Asp Ile Tyr Glu Gly Gln Ile Thr		
	500	505	510
	Ala Ile Leu Gly His Ser Gly Ala Gly Lys Ser Thr Leu Leu Asn Ile		
	515	520	525
25	Leu Ser Gly Leu Ser Val Pro Thr Lys Gly Ser Val Thr Ile Tyr Asn		
	530	535	540
30	Asn Lys Leu Ser Glu Met Ala Asp Leu Glu Asn Leu Ser Lys Leu Thr		
	545	550	555
	Gly Val Cys Pro Gln Ser Asn Val Gln Phe Asp Phe Leu Thr Val Arg		
	565	570	575
35	Glu Asn Leu Arg Leu Phe Ala Lys Ile Lys Gly Ile Leu Pro Gln Glu		
	580	585	590
40	Val Asp Lys Glu Ile Phe Leu Leu Asp Glu Pro Thr Ala Gly Leu Asp		
	595	600	605
	Pro Phe Ser Arg His Gln Val Trp Asn Leu Leu Lys Glu Arg Lys Thr		
	610	615	620
45	Asp Arg Val Ile Leu Phe Ser Thr Gln Phe Met Asp Glu Ala Asp Ile		
	625	630	635
	Leu Ala Asp Arg Lys Val Phe Leu Ser Gln Gly Lys Leu Lys Cys Ala		
50	645	650	655
	Gly Ser Ser Leu Phe Leu Lys Lys Trp Gly Ile Gly Tyr His Leu		
	660	665	670
55	Ser Leu Gln Leu Asn Glu Ile Cys Val Glu Glu Asn Ile Thr Ser Leu		

EP 1 217 066 A1

	675	680	685
5	Val Lys Gln His Ile Pro Asp Ala Lys Leu Ser Ala Lys Ser Glu Gly 690	695	700
	Lys Leu Ile Tyr Thr Leu Pro Leu Glu Arg Thr Asn Lys Phe Pro Glu 705	710	715
10	Leu Tyr Lys Asp Leu Asp Ser Tyr Pro Asp Leu Gly Ile Glu Asn Tyr 725	730	735
15	Gly Val Ser Met Thr Thr Leu Asn Glu Val Phe Leu Lys Leu Glu Gly 740	745	750
	Lys Ser Thr Ile Asn Glu Ser Asp Ile Ala Ile Leu Gly Glu Val Gln 755	760	765
20	Ala Glu Lys Ala Asp Asp Thr Glu Arg Leu Val Glu Met Glu Gln Val 770	775	780
	Leu Ser Ser Leu Asn Lys Met Arg Lys Thr Ile Gly Gly Val Ala Leu 785	790	795
25	Trp Arg Gln Gln Ile Cys Ala Ile Ala Arg Val Arg Leu Leu Lys Leu 805	810	815
	Lys His Glu Arg Lys Ala Leu Leu Ala Leu Leu Ile Leu Met Ala 820	825	830
30	Gly Phe Cys Pro Leu Leu Val Glu Tyr Thr Met Val Lys Ile Tyr Gln 835	840	845
	Asn Ser Tyr Thr Trp Glu Leu Ser Pro His Leu Tyr Phe Leu Ala Pro 850	855	860
35	Gly Gln Gln Pro His Asp Pro Leu Thr Gln Leu Leu Ile Ile Asn Lys 865	870	875
	Thr Gly Ala Ser Ile Asp Asp Phe Ile Gln Ser Val Glu His Gln Asn 885	890	895
40	Ile Ala Leu Glu Val Asp Ala Phe Gly Thr Arg Asn Gly Thr Asp Asp 900	905	910
	Pro Ser Tyr Asn Gly Ala Ile Thr Val Cys Cys Asn Glu Lys Asn Tyr 915	920	925
45	Ser Phe Ser Leu Ala Cys Asn Ala Lys Arg Leu Asn Cys Phe Pro Val		

EP 1 217 066 A1

	930	935	940
5	Leu Met Asp Ile Val Ser Asn Gly Leu Leu Gly Met Val Lys Pro Ser		
	945	950	955
	Val His Ile Arg Thr Glu Arg Ser Thr Phe Leu Glu Asn Gly Gln Asp		
	965	970	975
10	Asn Pro Ile Gly Phe Leu Ala Tyr Ile Met Phe Trp Leu Val Leu Thr		
	980	985	990
15	Ser Ser Cys Pro Pro Tyr Ile Ala Met Ser Ser Ile Asp Asp Tyr Lys		
	995	1000	1005
	Asn Arg Ala Arg Ser Gln Leu Arg Ile Ser Gly Leu Ser Pro Ser Ala		
20	1010	1015	1020
	Tyr Trp Phe Gly Gln Alà Leu Val Asp Val Ser Leu Tyr Phe Leu Val		
	1025	1030	1035
	1040		
25	Phe Val Phe Ile Tyr Leu Met Ser Tyr Ile Ser Asn Phe Glu Asp Met		
	1045	1050	1055
	Leu Leu Thr Ile Ile His Ile Ile Gln Ile Pro Cys Ala Val Gly Tyr		
30	1060	1065	1070
	Ser Phe Ser Leu Ile Phe Met Thr Tyr Val Ile Ser Phe Ile Phe Arg		
	1075	1080	1085
35	Lys Gly Arg Lys Asn Ser Gly Ile Trp Ser Phe Cys Phe Tyr Val Val		
	1090	1095	1100
	Thr Val Phe Ser Val Ala Gly Phe Ala Phe Ser Ile Phe Glu Ser Asp		
40	1105	1110	1115
	1120		
	Ile Pro Phe Ile Phe Thr Phe Leu Ile Pro Pro Ala Thr Met Ile Gly		
	1125	1130	1135
45	Cys Leu Phe Leu Ser Ser His Leu Leu Phe Ser Ser Leu Phe Ser Glu		
	1140	1145	1150
	Glu Arg Met Asp Val Gln Pro Phe Leu Val Phe Leu Ile Pro Phe Leu		
50	1155	1160	1165
	His Phe Ile Ile Phe Leu Phe Thr Leu Arg Cys Leu Glu Trp Lys Phe		
	1170	1175	1180
55	Gly Lys Lys Ser Met Arg Lys Asp Pro Phe Phe Arg Ile Ser Pro Arg		

EP 1 217 066 A1

	1185	1190	1195	1200
5	Ser Ser Asp Val Cys Gln Asn Pro Glu Glu Pro Glu Gly Glu Asp Glu			
	1205		1210	1215
	Asp Val Gln Met Glu Arg Val Arg Thr Ala Asn Ala Leu Asn Ser Thr			
	1220		1225	1230
10	Asn Phe Asp Glu Lys Pro Val Ile Ile Ala Ser Cys Leu Arg Lys Glu			
	1235	1240	1245	
15	Tyr Ala Gly Lys Arg Lys Gly Cys Phe Ser Lys Arg Lys Asn Lys Ile			
	1250	1255	1260	
	Ala Thr Arg Asn Val Ser Phe Cys Val Arg Lys Gly Glu Val Leu Gly			
20	1265	1270	1275	1280
	Leu Leu Gly His Asn Gly Ala Gly Lys Ser Thr Ser Ile Lys Val Ile			
	1285		1290	1295
25	Thr Gly Asp Thr Lys Pro Thr Ala Gly Gln Val Leu Leu Lys Gly Ser			
	1300	1305	1310	
	Gly Gly Gly Asp Ala Leu Glu Phe Leu Gly Tyr Cys Pro Gln Glu Asn			
30	1315	1320	1325	
	Ala Leu Trp Pro Asn Leu Thr Val Arg Gln His Leu Glu Val Tyr Ala			
	1330	1335	1340	
35	Ala Val Lys Gly Leu Arg Lys Gly Asp Ala Glu Val Ala Ile Thr Arg			
	1345	1350	1355	1360
	Leu Val Asp Ala Leu Lys Leu Gln Asp Gln Leu Lys Ser Pro Val Lys			
40	1365	1370	1375	
	Thr Leu Ser Glu Gly Ile Lys Arg Lys Leu Cys Phe Val Leu Ser Ile			
	1380	1385	1390	
45	Leu Gly Asn Pro Ser Val Val Leu Leu Asp Glu Pro Ser Thr Gly Met			
	1395	1400	1405	
	Asp Pro Glu Gly Gln Gln Met Trp Gln Ala Ile Arg Ala Thr Phe			
50	1410	1415	1420	
	Arg Asn Thr Glu Arg Gly Ala Leu Leu Thr Thr His Tyr Met Ala Glu			
	1425	1430	1435	1440
55	Ala Glu Ala Val Cys Asp Arg Val Ala Ile Met Val Ser Gly Arg Leu			

EP 1 217 066 A1

	1445	1450	1455
5	Arg Cys Ile Gly Ser Ile Gln His Leu Lys Ser Lys Phe Gly Lys Asp 1460	1465	1470
10	Tyr Leu Leu Glu Met Lys Val Lys Asn Leu Ala Gln Val Glu Pro Leu 1475	1480	1485
15	His Ala Glu Ile Leu Arg Leu Phe Pro Gln Ala Ala Arg Gln Glu Arg 1490	1495	1500
20	Tyr Ser Ser Leu Met Val Tyr Lys Leu Pro Val Glu Asp Val Gln Pro 1505	1510	1515
25	Leu Ala Gln Ala Phe Phe Lys Leu Glu Lys Val Lys Gln Ser Phe Asp 1525	1530	1535
30	Leu Glu Glu Tyr Ser Leu Ser Gln Ser Thr Leu Glu Gln Val Phe Leu 1540	1545	1550
35	Glu Leu Ser Lys Glu Gln Glu Leu Gly Asp Phe Glu Glu Asp Phe Asp 1555	1560	1565
40	Pro Ser Val Lys Trp Lys Leu Leu Pro Gln Glu Glu Pro 1570	1575	1580
45	<210> 50 <211> 1279 <212> PRT <213> Homo sapiens		
50	<400> 50 Met Asp Leu Glu Gly Asp Arg Asn Gly Gly Ala Lys Lys Lys Asn Phe 1 5 10 15		
55	Phe Lys Leu Asn Asn Lys Ser Glu Lys Asp Lys Lys Glu Lys Lys Pro 20 25 30		
60	Thr Val Ser Val Phe Ser Met Phe Arg Tyr Ser Asn Trp Leu Asp Lys 35 40 45		
65	Leu Tyr Met Val Val Gly Thr Leu Ala Ala Ile Ile His Gly Ala Gly 50 55 60		
70	Leu Pro Leu Met Met Leu Val Phe Gly Glu Met Thr Asp Ile Phe Ala 65 70 75 80		

EP 1 217 066 A1

	Asn Ala Gly Asn Leu Glu Asp Leu Met Ser Asn Ile Thr Asn Arg Ser			
5	85	90	95	
	Asp Ile Asn Asp Thr Gly Phe Phe Met Asn Leu Glu Glu Asp Met Thr			
	100	105	110	
10	Arg Tyr Ala Tyr Tyr Ser Gly Ile Gly Ala Gly Val Leu Val Ala			
	115	120	125	
15	Ala Tyr Ile Gln Val Ser Phe Trp Cys Leu Ala Ala Gly Arg Gln Ile			
	130	135	140	
	His Lys Ile Arg Lys Gln Phe Phe His Ala Ile Met Arg Gln Glu Ile			
	145	150	155	160
20	Gly Trp Phe Asp Val His Asp Val Gly Glu Leu Asn Thr Arg Leu Thr			
	165	170	175	
25	Asp Asp Val Ser Lys Ile Asn Glu Gly Ile Gly Asp Lys Ile Gly Met			
	180	185	190	
	Phe Phe Gln Ser Met Ala Thr Phe Phe Thr Gly Phe Ile Val Gly Phe			
	195	200	205	
30	Thr Arg Gly Trp Lys Leu Thr Leu Val Ile Leu Ala Ile Ser Pro Val			
	210	215	220	
35	Leu Gly Leu Ser Ala Ala Val Trp Ala Lys Ile Leu Ser Ser Phe Thr			
	225	230	235	240
	Asp Lys Glu Leu Leu Ala Tyr Ala Lys Ala Gly Ala Val Ala Glu Glu			
	245	250	255	
40	Val Leu Ala Ala Ile Arg Thr Val Ile Ala Phe Gly Gly Gln Lys Lys			
	260	265	270	
45	Glu Leu Glu Arg Tyr Asn Lys Asn Leu Glu Ala Lys Arg Ile Gly			
	275	280	285	
	Ile Lys Lys Ala Ile Thr Ala Asn Ile Ser Ile Gly Ala Ala Phe Leu			
	290	295	300	
50	Leu Ile Tyr Ala Ser Tyr Ala Leu Ala Phe Trp Tyr Gly Thr Thr Leu			
	305	310	315	320
55	Val Leu Ser Gly Glu Tyr Ser Ile Gly Gln Val Leu Thr Val Phe Ser			
	325	330	335	

EP 1 217 066 A1

Val Leu Ile Gly Ala Phe Ser Val Gly Gln Ala Ser Pro Ser Ile Glu
340 345 350

5

Ala Phe Ala Asn Ala Arg Gly Ala Ala Tyr Glu Ile Phe Lys Ile Ile
355 360 365

10 Asp Asn Lys Pro Ser Ile Asp Ser Tyr Ser Lys Ser Gly His Lys Pro
370 375 380

Asp Asn Ile Lys Gly Asn Leu Glu Phe Arg Asn Val His Phe Ser Tyr
15 385 390 395 400

Pro Ser Arg Lys Glu Val Lys Ile Leu Lys Gly Leu Asn Leu Lys Val
20 405 410 415

Gln Ser Gly Gln Thr Val Ala Leu Val Gly Asn Ser Gly Cys Gly Lys
420 425 430

Ser Thr Thr Val Gln Leu Met Gln Arg Leu Tyr Asp Pro Thr Glu Gly
25 435 440 445

Met Val Ser Val Asp Gly Gln Asp Ile Arg Thr Ile Asn Val Arg Phe
450 455 460

30 Leu Arg Glu Ile Ile Gly Val Val Ser Gln Glu Pro Val Leu Phe Ala
465 470 475 480

Thr Thr Ile Ala Glu Asn Ile Arg Tyr Gly Arg Glu Asn Val Thr Met
35 485 490 495

Asp Glu Ile Glu Lys Ala Val Lys Glu Ala Asn Ala Tyr Asp Phe Ile
40 500 505 510

Met Lys Leu Pro His Lys Phe Asp Thr Leu Val Gly Glu Arg Gly Ala
45 515 520 525

Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Leu
45 530 535 540

Val Arg Asn Pro Lys Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu
50 545 550 555 560

Asp Thr Glu Ser Glu Ala Val Val Gln Val Ala Leu Asp Lys Ala Arg
55 565 570 575

Lys Gly Arg Thr Thr Ile Val Ile Ala His Arg Leu Ser Thr Val Arg
55 580 585 590

EP 1 217 066 A1

Asn Ala Asp Val Ile Ala Gly Phe Asp Asp Gly Val Ile Val Glu Lys
5 595 600 605

Gly Asn His Asp Glu Leu Met Lys Glu Lys Gly Ile Tyr Phe Lys Leu
610 615 620

10 Val Thr Met Gln Thr Ala Gly Asn Glu Val Glu Leu Glu Asn Ala Ala
625 630 635 640

Asp Glu Ser Lys Ser Glu Ile Asp Ala Leu Glu Met Ser Ser Asn Asp
15 645 650 655

Ser Arg Ser Ser Leu Ile Arg Lys Arg Ser Thr Arg Arg Ser Val Arg
660 665 670

20 Gly Ser Gln Ala Gln Asp Arg Lys Leu Ser Thr Lys Glu Ala Leu Asp
675 680 685

Glu Ser Ile Pro Pro Val Ser Phe Trp Arg Ile Met Lys Leu Asn Leu
25 690 695 700

Thr Glu Trp Pro Tyr Phe Val Val Gly Val Phe Cys Ala Ile Ile Asn
705 710 715 720

30 Gly Gly Leu Gln Pro Ala Phe Ala Ile Ile Phe Ser Lys Ile Ile Gly
725 730 735

Val Phe Thr Arg Ile Asp Asp Pro Glu Thr Lys Arg Gln Asn Ser Asn
35 740 745 750

Leu Phe Ser Leu Leu Phe Leu Ala Leu Gly Ile Ile Ser Phe Ile Thr
755 760 765

40 Phe Phe Leu Gln Gly Phe Thr Phe Gly Lys Ala Gly Glu Ile Leu Thr
770 775 780

Lys Arg Leu Arg Tyr Met Val Phe Arg Ser Met Leu Arg Gln Asp Val
45 785 790 795 800

Ser Trp Phe Asp Asp Pro Lys Asn Thr Thr Gly Ala Leu Thr Thr Arg
805 810 815

50 Leu Ala Asn Asp Ala Ala Gln Val Lys Gly Ala Ile Gly Ser Arg Leu
820 825 830

55 Ala Val Ile Thr Gln Asn Ile Ala Asn Leu Gly Thr Gly Ile Ile Ile
835 840 845

Ser Phe Ile Tyr Gly Trp Gln Leu Thr Leu Leu Leu Ala Ile Val
 850 855 860
 5

Pro Ile Ile Ala Ile Ala Gly Val Val Glu Met Lys Met Leu Ser Gly
 865 870 875 880

10 Gln Ala Leu Lys Asp Lys Lys Glu Leu Glu Gly Ser Gly Lys Ile Ala
 885 890 895

15 Thr Glu Ala Ile Glu Asn Phe Arg Thr Val Val Ser Leu Thr Gln Glu
 900 905 910

Gln Lys Phe Glu His Met Tyr Ala Gln Ser Leu Gln Val Pro Tyr Arg
 915 920 925

20 Asn Ser Leu Arg Lys Ala His Ile Phe Gly Ile Thr Phe Ser Phe Thr
 930 935 940

25 Gln Ala Met Met Tyr Phe Ser Tyr Ala Gly Cys Phe Arg Phe Gly Ala
 945 950 955 960

Tyr Leu Val Ala His Lys Leu Met Ser Phe Glu Asp Val Leu Leu Val
 965 970 975

30 Phe Ser Ala Val Val Phe Gly Ala Met Ala Val Gly Gln Val Ser Ser
 980 985 990

35 Phe Ala Pro Asp Tyr Ala Lys Ala Lys Ile Ser Ala Ala His Ile Ile
 995 1000 1005

Met Ile Ile Glu Lys Thr Pro Leu Ile Asp Ser Tyr Ser Thr Glu Gly
 1010 1015 1020

40 Leu Met Pro Asn Thr Leu Glu Gly Asn Val Thr Phe Gly Glu Val Val
 1025 1030 1035 1040

45 Phe Asn Tyr Pro Thr Arg Pro Asp Ile Pro Val Leu Gln Gly Leu Ser
 1045 1050 1055

Leu Glu Val Lys Lys Gly Gln Thr Leu Ala Leu Val Gly Ser Ser Gly
 1060 1065 1070

50 Cys Gly Lys Ser Thr Val Val Gln Leu Leu Glu Arg Phe Tyr Asp Pro
 1075 1080 1085

55 Leu Ala Gly Lys Val Leu Leu Asp Gly Lys Glu Ile Lys Arg Leu Asn
 1090 1095 1100

EP 1 217 066 A1

Val Gln Trp Leu Arg Ala His Leu Gly Ile Val Ser Gln Glu Pro Ile
1105 1110 1115 1120
5

Leu Phe Asp Cys Ser Ile Ala Glu Asn Ile Ala Tyr Gly Asp Asn Ser
1125 1130 1135

10 Arg Val Val Ser Gln Glu Glu Ile Val Arg Ala Ala Lys Glu Ala Asn
1140 1145 1150

Ile His Ala Phe Ile Glu Ser Leu Pro Asn Lys Tyr Ser Thr Lys Val
1155 1160 1165
15

Gly Asp Lys Gly Thr Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile Ala
1170 1175 1180

20 Ile Ala Arg Ala Leu Val Arg Gln Pro His Ile Leu Leu Leu Asp Glu
1185 1190 1195 1200

Ala Thr Ser Ala Leu Asp Thr Glu Ser Glu Lys Val Val Gln Glu Ala
25 1205 1210 1215

Leu Asp Lys Ala Arg Glu Gly Arg Thr Cys Ile Val Ile Ala His Arg
1220 1225 1230

30 Leu Ser Thr Ile Gln Asn Ala Asp Leu Ile Val Val Phe Gln Asn Gly
1235 1240 1245

Arg Val Lys Glu His Gly Thr His Gln Gln Leu Leu Ala Gln Lys Gly
35 1250 1255 1260

Ile Tyr Phe Ser Met Val Ser Val Gln Ala Gly Thr Lys Arg Gln
1265 1270 1275
40

<210> 51
45 <211> 808
<212> PRT
<213> Homo sapiens

<400> 51
50 Met Ala Glu Leu Leu Ala Ser Ala Gly Ser Ala Cys Ser Trp Asp Phe
1 5 10 15

Pro Arg Ala Pro Pro Ser Phe Pro Pro Pro Ala Ala Ser Arg Gly Gly
55 20 25 30

EP 1 217 066 A1

Leu Gly Gly Thr Arg Ser Phe Arg Pro His Arg Gly Ala Glu Ser Pro
35 40 45

5 Arg Pro Gly Arg Asp Arg Asp Gly Val Arg Val Pro Met Ala Ser Ser
50 55 60

10 Arg Cys Pro Ala Pro Arg Gly Cys Arg Cys Leu Pro Gly Ala Ser Leu
15 65 70 75 80

Ala Trp Leu Gly Thr Val Leu Leu Leu Ala Asp Trp Val Leu Leu
15 85 90 95

Arg Thr Ala Leu Pro Arg Ile Phe Ser Leu Leu Val Pro Thr Ala Leu
20 100 105 110

Pro Leu Leu Arg Val Trp Ala Val Gly Leu Ser Arg Trp Ala Val Leu
25 115 120 125

Trp Leu Gly Ala Cys Gly Val Leu Arg Ala Thr Val Gly Ser Lys Ser
30 130 135 140

Glu Asn Ala Gly Ala Gln Gly Trp Leu Ala Ala Leu Lys Pro Leu Ala
35 145 150 155 160

Ala Ala Leu Gly Leu Ala Leu Pro Gly Leu Ala Leu Phe Arg Glu Leu
40 165 170 175

Ile Ser Trp Gly Ala Pro Gly Ser Ala Asp Ser Thr Arg Leu Leu His
45 180 185 190

Trp Gly Ser His Pro Thr Ala Phe Val Val Ser Tyr Ala Ala Ala Leu
50 195 200 205

Pro Ala Ala Ala Leu Trp His Lys Leu Gly Ser Leu Trp Val Pro Gly
55 210 215 220

Gly Gln Gly Gly Ser Gly Asn Pro Val Arg Arg Leu Leu Gly Cys Leu
60 225 230 235 240

Gly Ser Glu Thr Arg Arg Leu Ser Leu Phe Leu Val Leu Val Val Leu
65 245 250 255

Ser Ser Leu Gly Glu Met Ala Ile Pro Phe Phe Thr Gly Arg Leu Thr
70 260 265 270

Asp Trp Ile Leu Gln Asp Gly Ser Ala Asp Thr Phe Thr Arg Asn Leu
75 275 280 285

EP 1 217 066 A1

Thr Leu Met Ser Ile Leu Thr Ile Ala Ser Ala Val Leu Glu Phe Val
 290 295 300

5 Gly Asp Gly Ile Tyr Asn Asn Thr Met Gly His Val His Ser His Leu
 305 310 315 320

Gln Gly Glu Val Phe Gly Ala Val Leu Arg Gln Glu Thr Glu Phe Phe
 10 325 330 335

Gln Gln Asn Gln Thr Gly Asn Ile Met Ser Arg Val Thr Glu Asp Thr
 340 345 350

15 Ser Thr Leu Ser Asp Ser Leu Ser Glu Asn Leu Ser Leu Phe Leu Trp
 355 360 365

20 Tyr Leu Val Arg Gly Leu Cys Leu Leu Gly Ile Met Leu Trp Gly Ser
 370 375 380

Val Ser Leu Thr Met Val Thr Leu Ile Thr Leu Pro Leu Leu Phe Leu
 385 390 395 400

25 Leu Pro Lys Lys Val Gly Lys Trp Tyr Gln Leu Leu Glu Val Gln Val
 405 410 415

30 Arg Glu Ser Leu Ala Lys Ser Ser Gln Val Ala Ile Glu Ala Leu Ser
 420 425 430

Ala Met Pro Thr Val Arg Ser Phe Ala Asn Glu Glu Gly Ala Gln
 435 440 445

35 Lys Phe Arg Glu Lys Leu Gln Glu Ile Lys Thr Leu Asn Gln Lys Glu
 450 455 460

40 Ala Val Ala Tyr Ala Val Asn Ser Trp Thr Thr Ser Ile Ser Gly Met
 465 470 475 480

Leu Leu Lys Val Gly Ile Leu Tyr Ile Gly Gly Gln Leu Val Thr Ser
 485 490 495

45 Gly Ala Val Ser Ser Gly Asn Leu Val Thr Phe Val Leu Tyr Gln Met
 500 505 510

50 Gln Phe Thr Gln Ala Val Glu Val Leu Leu Ser Ile Tyr Pro Arg Val
 515 520 525

Gln Lys Ala Val Gly Ser Ser Glu Lys Ile Phe Glu Tyr Leu Asp Arg
 55 530 535 540

EP 1 217 066 A1

Thr Pro Arg Cys Pro Pro Ser Gly Leu Leu Thr Pro Leu His Leu Glu
545 550 555 560

5 Gly Leu Val Gln Phe Gln Asp Val Ser Phe Ala Tyr Pro Asn Arg Pro
565 570 575

Asp Val Leu Val Leu Gln Gly Leu Thr Phe Thr Leu Arg Pro Gly Glu
10 580 585 590

Val Thr Ala Leu Val Gly Pro Asn Gly Ser Gly Lys Ser Thr Val Ala
595 600 605

15 Ala Leu Leu Gln Asn Leu Tyr Gln Pro Thr Gly Gly Gln Leu Leu Leu
610 615 620

Asp Gly Lys Pro Leu Pro Gln Tyr Glu His Arg Tyr Leu His Arg Gln
20 625 630 635 640

Val Ala Ala Val Gly Gln Glu Pro Gln Val Phe Gly Arg Ser Leu Gln
645 650 655

25 Glu Asn Ile Ala Tyr Gly Leu Thr Gln Lys Pro Thr Met Glu Glu Ile
660 665 670

Thr Ala Ala Ala Val Lys Ser Gly Ala His Ser Phe Ile Ser Gly Leu
30 675 680 685

Pro Gln Gly Tyr Asp Thr Glu Val Asp Glu Ala Gly Ser Gln Leu Ser
35 690 695 700

Gly Gly Gln Arg Gln Ala Val Ala Leu Ala Arg Ala Leu Ile Arg Lys
705 710 715 720

40 Pro Cys Val Leu Ile Leu Asp Asp Ala Thr Ser Ala Leu Asp Ala Asn
725 730 735

Ser Gln Leu Gln Val Glu Gln Leu Leu Tyr Glu Ser Pro Glu Arg Tyr
45 740 745 750

Ser Arg Ser Val Leu Leu Ile Thr Gln His Leu Ser Leu Val Glu Gln
755 760 765

50 Ala Asp His Ile Leu Phe Leu Glu Gly Gly Ala Ile Arg Glu Gly Gly
770 775 780

55 Thr His Gln Gln Leu Met Glu Lys Lys Gly Cys Tyr Trp Ala Met Val
785 790 795 800

Gln Ala Pro Ala Asp Ala Pro Glu
805

5

<210> 52

<211> 808

10 <212> PRT

<213> Homo sapiens

<400> 52

15 Met Ala Glu Leu Leu Ala Ser Ala Gly Ser Ala Cys Ser Trp Asp Phe
1 5 10 1520 Pro Arg Ala Pro Pro Ser Phe Pro Pro Pro Ala Ala Ser Arg Gly Gly
20 25 30

20

Leu Gly Gly Thr Arg Ser Phe Arg Pro His Arg Gly Ala Glu Ser Pro
35 40 45

25

Arg Pro Gly Arg Asp Arg Asp Gly Val Arg Val Pro Met Ala Ser Ser
50 55 60

30

Arg Cys Pro Ala Pro Arg Gly Cys Arg Cys Leu Pro Gly Ala Ser Leu
65 70 75 80Ala Trp Leu Gly Thr Val Leu Leu Leu Ala Asp Trp Val Leu Leu
85 90 95

35

Arg Thr Ala Leu Pro Arg Ile Phe Ser Leu Leu Val Pro Thr Ala Leu
100 105 110

40

Pro Leu Leu Arg Val Trp Ala Val Gly Leu Ser Arg Trp Ala Val Leu
115 120 125Trp Leu Gly Ala Cys Gly Val Leu Arg Ala Thr Val Gly Ser Lys Ser
130 135 140

45

Glu Asn Ala Gly Ala Gln Gly Trp Leu Ala Ala Leu Lys Pro Leu Ala
145 150 155 160

50

Ala Ala Leu Gly Leu Ala Leu Pro Gly Leu Ala Leu Phe Arg Glu Leu
165 170 175Ile Ser Trp Gly Ala Pro Gly Ser Ala Asp Ser Thr Arg Leu Leu His
180 185 190

55

Trp Gly Ser His Pro Thr Ala Phe Val Val Ser Tyr Ala Ala Leu

EP 1217066 A1

	195	200	205
5	Pro Ala Ala Ala Leu Trp His Lys Leu Gly Ser Leu Trp Val Pro Gly		
	210	215	220
10	Gly Gln Gly Gly Ser Gly Asn Pro Val Arg Arg Leu Leu Gly Cys Leu		
	225	230	235
	240		
15	Gly Ser Glu Thr Arg Arg Leu Ser Leu Phe Leu Val Leu Val Val Leu		
	245	250	255
20	Ser Ser Leu Gly Glu Met Ala Ile Pro Phe Phe Thr Gly Arg Leu Thr		
	260	265	270
25	Asp Trp Ile Leu Gln Asp Gly Ser Ala Asp Thr Phe Thr Arg Asn Leu		
	275	280	285
30	Thr Leu Met Ser Ile Leu Thr Ile Ala Ser Ala Val Leu Glu Phe Val		
	290	295	300
35	Gly Asp Gly Ile Tyr Asn Asn Thr Met Gly His Val His Ser His Leu		
	305	310	315
	320		
40	Gln Gly Glu Val Phe Gly Ala Val Leu Arg Gln Glu Thr Glu Phe Phe		
	325	330	335
45	Gln Gln Asn Gln Thr Gly Asn Ile Met Ser Arg Val Thr Glu Asp Thr		
	340	345	350
50	Ser Thr Leu Ser Asp Ser Leu Ser Glu Asn Leu Ser Leu Phe Leu Trp		
	355	360	365
55	Tyr Leu Val Arg Gly Leu Cys Leu Leu Gly Ile Met Leu Trp Gly Ser		
	370	375	380
	Val Ser Leu Thr Met Val Thr Leu Ile Thr Leu Pro Leu Leu Phe Leu		
	385	390	395
	400		
	Leu Pro Lys Lys Val Gly Lys Trp Tyr Gln Leu Leu Glu Val Gln Val		
	405	410	415
	Arg Glu Ser Leu Ala Lys Ser Ser Gln Val Ala Ile Glu Ala Leu Ser		
	420	425	430
	Ala Met Pro Thr Val Arg Ser Phe Ala Asn Glu Glu Gly Glu Ala Gln		
	435	440	445
	Lys Phe Arg Glu Lys Leu Gln Glu Ile Lys Thr Leu Asn Gln Lys Glu		

EP 1 217 066 A1

	450	455	460
5	Ala Val Ala Tyr Ala Val Asn Ser Trp Thr Thr Ser Ile Ser Gly Met		
	465	470	475
	Leu Leu Lys Val Gly Ile Leu Tyr Ile Gly Gly Gln Leu Val Thr Ser		
	485	490	495
10	Gly Ala Val Ser Ser Gly Asn Leu Val Thr Phe Val Leu Tyr Gln Met		
	500	505	510
15	Gln Phe Thr Gln Ala Val Glu Val Leu Leu Ser Ile Tyr Pro Arg Val		
	515	520	525
	Gln Lys Ala Val Gly Ser Ser Glu Lys Ile Phe Glu Tyr Leu Asp Arg		
	530	535	540
20	Thr Pro Arg Cys Pro Pro Ser Gly Leu Leu Thr Pro Leu His Leu Glu		
	545	550	555
	560		
25	Gly Leu Val Gln Phe Gln Asp Val Ser Phe Ala Tyr Pro Asn Arg Pro		
	565	570	575
	Asp Val Leu Val Leu Gln Gly Leu Thr Phe Thr Leu Arg Pro Gly Glu		
	580	585	590
30	Val Thr Ala Leu Val Gly Pro Asn Gly Ser Gly Lys Ser Thr Val Ala		
	595	600	605
35	Ala Leu Leu Gln Asn Leu Tyr Gln Pro Thr Gly Gly Gln Leu Leu		
	610	615	620
	Asp Gly Lys Pro Leu Pro Gln Tyr Glu His Arg Tyr Leu His Arg Gln		
	625	630	635
	640		
	Val Ala Ala Val Gly Gln Glu Pro Gln Val Phe Gly Arg Ser Leu Gln		
	645	650	655
45	Glu Asn Ile Ala Tyr Gly Leu Thr Gln Lys Pro Thr Met Glu Glu Ile		
	660	665	670
	Thr Ala Ala Ala Val Lys Ser Gly Ala His Ser Phe Ile Ser Gly Leu		
	675	680	685
	Pro Gln Gly Tyr Asp Thr Glu Val Asp Glu Ala Gly Ser Gln Leu Ser		
	690	695	700
55	Gly Gly Gln Arg Gln Ala Val Ala Leu Ala Arg Ala Leu Ile Arg Lys		

EP 1 217 066 A1

705	710	715	720
Pro Cys Val Leu Ile Leu Asp Asp Ala Thr Ser Ala Leu Asp Ala Asn			
5	725	730	735
Ser Gln Leu Gln Val Glu Gln Leu Leu Tyr Glu Ser Pro Glu Arg Tyr			
	740	745	750
10	Ser Arg Ser Val Leu Leu Ile Thr Gln His Leu Ser Leu Val Glu Gln		
	755	760	765
15	Ala Asp His Ile Leu Phe Leu Glu Gly Gly Ala Ile Arg Glu Gly Gly		
	770	775	780
Thr His Gln Gln Leu Met Glu Lys Lys Gly Cys Tyr Trp Ala Met Val			
20	785	790	795
Gln Ala Pro Ala Asp Ala Pro Glu			
	805		
25	<210> 53		
	<211> 1232		
30	<212> PRT		
	<213> Homo sapiens		
<400> 53			
35	Met Asp Leu Glu Ala Ala Lys Asn Gly Thr Ala Trp Arg Pro Thr Ser		
	1	5	10
	15		
Ala Glu Gly Asp Phe Glu Leu Gly Ile Ser Ser Lys Gln Lys Arg Lys			
	20	25	30
40	Lys Thr Lys Thr Val Lys Met Ile Gly Val Leu Thr Leu Phe Arg Tyr		
	35	40	45
45	Ser Asp Trp Gln Asp Lys Leu Phe Met Ser Leu Gly Thr Ile Met Ala		
	50	55	60
Ile Ala His Gly Ser Gly Leu Pro Leu Met Met Ile Val Phe Gly Glu			
50	65	70	75
			80
Met Thr Asp Lys Phe Val Asp Thr Ala Gly Asn Phe Ser Phe Pro Val			
	85	90	95
55	Asn Phe Ser Leu Ser Leu Leu Asn Pro Gly Lys Ile Leu Glu Glu Glu		
	100	105	110

Met Thr Arg Tyr Ala Tyr Tyr Tyr Ser Gly Leu Gly Ala Gly Val Leu
 115 120 125
 5

Val Ala Ala Tyr Ile Gln Val Ser Phe Trp Thr Leu Ala Ala Gly Arg
 130 135 140

10 Gln Ile Arg Lys Ile Arg Gln Lys Phe Phe His Ala Ile Leu Arg Gln
 145 150 155 160

15 Glu Ile Gly Trp Phe Asp Ile Asn Asp Thr Thr Glu Leu Asn Thr Arg
 165 170 175

Leu Thr Asp Asp Ile Ser Lys Ile Ser Glu Gly Ile Gly Asp Lys Val
 180 185 190

20 Gly Met Phe Phe Gln Ala Val Ala Thr Phe Phe Ala Gly Phe Ile Val
 195 200 205

25 Gly Phe Ile Arg Gly Trp Lys Leu Thr Leu Val Ile Met Ala Ile Ser
 210 215 220

Pro Ile Leu Gly Leu Ser Ala Ala Val Trp Ala Lys Ile Leu Ser Ala
 225 230 235 240

30 Phe Ser Asp Lys Glu Leu Ala Ala Tyr Ala Lys Ala Gly Ala Val Ala
 245 250 255

35 Glu Glu Ala Leu Gly Ala Ile Arg Thr Val Ile Ala Phe Gly Gly Gln
 260 265 270

Asn Lys Glu Leu Glu Arg Tyr Gln Lys His Leu Glu Asn Ala Lys Glu
 275 280 285

40 Ile Gly Ile Lys Lys Ala Ile Ser Ala Asn Ile Ser Met Gly Ile Ala
 290 295 300

45 Phe Leu Leu Ile Tyr Ala Ser Tyr Ala Leu Ala Phe Trp Tyr Gly Ser
 305 310 315 320

Thr Leu Val Ile Ser Lys Glu Tyr Thr Ile Gly Asn Ala Met Thr Val
 325 330 335

50 Phe Phe Ser Ile Leu Ile Gly Ala Phe Ser Val Gly Gln Ala Ala Pro
 340 345 350

55 Cys Ile Asp Ala Phe Ala Asn Ala Arg Gly Ala Ala Tyr Val Ile Phe
 355 360 365

EP 1 217 066 A1

Asp Ile Ile Asp Asn Asn Pro Lys Ile Asp Ser Phe Ser Glu Arg Gly
370 375 380
5

His Lys Pro Asp Ser Ile Lys Gly Asn Leu Glu Phe Asn Asp Val His
385 390 395 400

10 Phe Ser Tyr Pro Ser Arg Ala Asn Val Lys Ile Leu Lys Gly Leu Asn
405 410 415

Leu Lys Val Gln Ser Gly Gln Thr Val Ala Leu Val Gly Ser Ser Gly
15 420 425 430

Cys Gly Lys Ser Thr Thr Val Gln Leu Ile Gln Arg Leu Tyr Asp Pro
435 440 445

20 Asp Glu Gly Thr Ile Asn Ile Asp Gly Gln Asp Ile Arg Asn Phe Asn
450 455 460

Val Asn Tyr Leu Arg Glu Ile Ile Gly Val Val Ser Gln Glu Pro Val
25 465 470 475 480

Leu Phe Ser Thr Thr Ile Ala Glu Asn Ile Cys Tyr Gly Arg Gly Asn
485 490 495

30 Val Thr Met Asp Glu Ile Lys Lys Ala Val Lys Glu Ala Asn Ala Tyr
500 505 510

Glu Phe Ile Met Lys Leu Pro Gln Lys Phe Asp Thr Leu Val Gly Glu
35 515 520 525

Arg Gly Ala Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala
530 535 540

40 Arg Ala Leu Val Arg Asn Pro Lys Ile Leu Leu Asp Glu Ala Thr
545 550 555 560

Ser Ala Leu Asp Thr Glu Ser Glu Ala Glu Val Gln Ala Ala Leu Asp
45 565 570 575

Lys Ala Arg Glu Gly Arg Thr Thr Ile Val Ile Ala His Arg Leu Ser
580 585 590

50 Thr Val Arg Asn Ala Asp Val Ile Ala Gly Phe Glu Asp Gly Val Ile
595 600 605

55 Val Glu Gln Gly Ser His Ser Glu Leu Met Lys Lys Glu Gly Val Tyr
610 615 620

EP 1 217 066 A1

Phe Lys Leu Val Asn Met Gln Thr Ser Gly Ser Gln Ile Gln Ser Glu
625 630 635 640
5

Glu Phe Glu Leu Asn Asp Glu Lys Ala Ala Thr Arg Met Ala Pro Asn
645 650 655

Gly Trp Lys Ser Arg Leu Phe Arg His Ser Thr Gln Lys Asn Leu Lys
10 660 665 670

Asn Ser Gln Met Cys Gln Lys Ser Leu Asp Val Glu Thr Asp Gly Leu
15 675 680 685

Glu Ala Asn Val Pro Pro Val Ser Phe Leu Lys Val Leu Lys Leu Asn
690 695 700

Lys Thr Glu Trp Pro Tyr Phe Val Val Gly Thr Val Cys Ala Ile Ala
20 705 710 715 720

Asn Gly Gly Leu Gln Pro Ala Phe Ser Val Ile Phe Ser Glu Ile Ile
25 725 730 735

Ala Ile Phe Gly Pro Gly Asp Asp Ala Val Lys Gln Gln Lys Cys Asn
740 745 750

Ile Phe Ser Leu Ile Phe Leu Phe Leu Gly Ile Ile Ser Phe Phe Thr
30 755 760 765

Phe Phe Leu Gln Gly Phe Thr Phe Gly Lys Ala Gly Glu Ile Leu Thr
35 770 775 780

Arg Arg Leu Arg Ser Met Ala Phe Lys Ala Met Leu Arg Gln Asp Met
785 790 795 800

Ser Trp Phe Asp Asp His Lys Asn Ser Thr Gly Ala Leu Ser Thr Arg
40 805 810 815

Leu Ala Thr Asp Ala Ala Gln Val Gln Gly Ala Thr Gly Thr Arg Leu
45 820 825 830

Ala Leu Ile Ala Gln Asn Ile Ala Asn Leu Gly Thr Gly Ile Ile Ile
50 835 840 845

Ser Phe Ile Tyr Gly Trp Gln Leu Thr Leu Leu Leu Ala Val Val
850 855 860

Pro Ile Ile Ala Val Ser Gly Ile Val Glu Met Lys Leu Leu Ala Gly
55 865 870 875 880

EP 1 217 066 A1

Asn Ala Lys Arg Asp Lys Lys Glu Leu Glu Ala Ala Gly Lys Ile Ala
 885 890 895
 5

Thr Glu Ala Ile Glu Asn Ile Arg Thr Val Val Ser Leu Thr Gln Glu
 900 905 910
 10

Arg Lys Phe Glu Ser Met Tyr Val Glu Lys Leu Tyr Gly Pro Tyr Arg
 915 920 925
 15

Val Phe Ser Ala Ile Val Phe Gly Ala Val Ala Leu Gly His Ala Ser
 930 935 940
 20

Ser Phe Ala Pro Asp Tyr Ala Lys Ala Lys Leu Ser Ala Ala His Leu
 945 950 955 960

25

Phe Met Leu Phe Glu Arg Gln Pro Leu Ile Asp Ser Tyr Ser Glu Glu
 965 970 975

Gly Leu Lys Pro Asp Lys Phe Glu Gly Asn Ile Thr Phe Asn Glu Val
 980 985 990

30

Val Phe Asn Tyr Pro Thr Arg Ala Asn Val Pro Val Leu Gln Gly Leu
 995 1000 1005

35

Ser Leu Glu Val Lys Lys Gly Gln Thr Leu Ala Leu Val Gly Ser Ser
 1010 1015 1020

40

Gly Cys Gly Lys Ser Thr Val Val Gln Leu Leu Glu Arg Phe Tyr Asp
 1025 1030 1035 1040

Pro Leu Ala Gly Thr Val Leu Leu Asp Gly Gln Glu Ala Lys Lys Leu
 1045 1050 1055

45

Asn Val Gln Trp Leu Arg Ala Gln Leu Gly Ile Val Ser Gln Glu Pro
 1060 1065 1070

Ile Leu Phe Asp Cys Ser Ile Ala Glu Asn Ile Ala Tyr Gly Asp Asn
 1075 1080 1085

50

Ser Arg Val Val Ser Gln Asp Glu Ile Val Ser Ala Ala Lys Ala Ala
 1090 1095 1100

Asn Ile His Pro Phe Ile Glu Thr Leu Pro His Lys Tyr Glu Thr Arg
 1105 1110 1115 1120

55

Val Gly Asp Lys Gly Thr Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile
 1125 1130 1135

EP 1 217 066 A1

Ala Ile Ala Arg Ala Leu Ile Arg Gln Pro Gln Ile Leu Leu Leu Asp
1140 1145 1150

5

Glu Ala Thr Ser Ala Leu Asp Thr Glu Ser Glu Lys Val Val Gln Glu
1155 1160 1165

10 Ala Leu Asp Lys Ala Arg Glu Gly Arg Thr Cys Ile Val Ile Ala His
1170 1175 1180

15 Arg Leu Ser Thr Ile Gln Asn Ala Asp Leu Ile Val Val Phe Gln Asn
1185 1190 1195 1200

Gly Arg Val Lys Glu His Gly Thr His Gln Gln Leu Leu Ala Gln Lys
1205 1210 1215

20 Gly Ile Tyr Phe Ser Met Val Ser Val Gln Ala Gly Thr Gln Asn Leu
1220 1225 1230

25

30 <210> 54
<211> 842
<212> PRT
<213> Homo sapiens

35 <400> 54
Met Val Thr Val Gly Asn Tyr Cys Glu Ala Glu Gly Pro Val Gly Pro
1 5 10 15

40 Ala Trp Met Gln Asp Gly Leu Ser Pro Cys Phe Phe Thr Leu Val
20 25 30

45 Pro Ser Thr Arg Met Ala Leu Gly Thr Leu Ala Leu Val Leu Ala Leu
35 40 45

50 Pro Cys Arg Arg Arg Glu Arg Pro Ala Gly Ala Asp Ser Leu Ser Trp
50 55 60

55 Gly Ala Gly Pro Arg Ile Ser Pro Tyr Val Leu Gln Leu Leu Ala
65 70 75 80

55 Thr Leu Gln Ala Ala Leu Pro Leu Ala Gly Leu Ala Gly Arg Val Gly
85 90 95

EP 1 217 066 A1

Thr Ala Arg Gly Ala Pro Leu Pro Ser Tyr Leu Leu Leu Ala Ser Val
100 105 110

5 Leu Glu Ser Leu Ala Gly Ala Cys Gly Leu Trp Leu Leu Val Val Glu
115 120 125

10 Arg Ser Gln Ala Arg Gln Arg Leu Ala Met Gly Ile Trp Ile Lys Phe
130 135 140

Arg His Ser Pro Gly Leu Leu Leu Leu Trp Thr Val Ala Phe Ala Ala
145 150 155 160

15 Glu Asn Leu Ala Leu Val Ser Trp Asn Ser Pro Gln Trp Trp Trp Ala
165 170 175

20 Arg Ala Asp Leu Gly Gln Gln Val Gln Phe Ser Leu Trp Val Leu Arg
180 185 190

Tyr Val Val Ser Gly Gly Leu Phe Val Leu Gly Leu Trp Ala Pro Gly
195 200 205

25 Leu Arg Pro Gln Ser Tyr Thr Leu Gln Val His Glu Glu Asp Gln Asp
210 215 220

30 Val Glu Arg Ser Gln Val Arg Ser Ala Ala Gln Gln Ser Thr Trp Arg
225 230 235 240

Asp Phe Gly Arg Lys Leu Arg Leu Leu Ser Gly Tyr Leu Trp Pro Arg
35 245 250 255

Gly Ser Pro Ala Leu Gln Leu Val Val Leu Ile Cys Leu Gly Leu Met
260 265 270

40 Gly Leu Glu Arg Ala Leu Asn Val Leu Val Pro Ile Phe Tyr Arg Asn
275 280 285

Ile Val Asn Leu Leu Thr Glu Lys Ala Pro Trp Asn Ser Leu Ala Trp
45 290 295 300

305 310 315 320

50 Gly Ser Thr Gly Phe Val Ser Asn Leu Arg Thr Phe Leu Trp Ile Arg
325 330 335

55 Val Gln Gln Phe Thr Ser Arg Arg Val Glu Leu Leu Ile Phe Ser His
340 345 350

EP 1 217 066 A1

	Leu His Glu Leu Ser Leu Arg Trp His Leu Gly Arg Arg Thr Gly Glu			
	355	360	365	
5	Val Leu Arg Ile Ala Asp Arg Gly Thr Ser Ser Val Thr Gly Leu Leu			
	370	375	380	
10	Ser Tyr Leu Val Phe Asn Val Ile Pro Thr Leu Ala Asp Ile Ile Ile			
	385	390	395	400
	Gly Ile Ile Tyr Phe Ser Met Phe Asn Ala Trp Phe Gly Leu Ile			
	405	410	415	
15	Val Phe Leu Cys Met Ser Leu Tyr Leu Thr Leu Thr Ile Val Val Thr			
	420	425	430	
20	Glu Trp Arg Thr Lys Phe Arg Arg Ala Met Asn Thr Gln Glu Asn Ala			
	435	440	445	
	Thr Arg Ala Arg Ala Val Asp Ser Leu Leu Asn Phe Glu Thr Val Lys			
	450	455	460	
25	Tyr Tyr Asn Ala Glu Ser Tyr Glu Val Glu Arg Tyr Arg Glu Ala Ile			
	465	470	475	480
30	Ile Lys Tyr Gln Gly Leu Glu Trp Lys Ser Ser Ala Ser Leu Val Leu			
	485	490	495	
	Leu Asn Gln Thr Gln Asn Leu Val Ile Gly Leu Gly Leu Leu Ala Gly			
35	500	505	510	
	Ser Leu Leu Cys Ala Tyr Phe Val Thr Glu Gln Lys Leu Gln Val Gly			
	515	520	525	
40	Asp Tyr Val Leu Phe Gly Thr Tyr Ile Ile Gln Leu Tyr Met Pro Leu			
	530	535	540	
	Asn Trp Phe Gly Thr Tyr Tyr Arg Met Ile Gln Thr Asn Phe Ile Asp			
45	545	550	555	560
	Met Glu Asn Met Phe Asp Leu Leu Lys Glu Glu Thr Glu Val Lys Asp			
	565	570	575	
50	Leu Pro Gly Ala Gly Pro Leu Arg Phe Gln Lys Gly Arg Ile Glu Phe			
	580	585	590	
	Glu Asn Val His Phe Ser Tyr Ala Asp Gly Arg Glu Thr Leu Gln Asp			
55	595	600	605	

EP 1 217 066 A1

Val Ser Phe Thr Val Met Pro Gly Gln Thr Leu Ala Leu Val Gly Pro
610 615 620

5 Ser Gly Ala Gly Lys Ser Thr Ile Leu Arg Leu Leu Phe Arg Phe Tyr
625 630 635 640

10 Asp Ile Ser Ser Gly Cys Ile Arg Ile Asp Gly Gln Asp Ile Ser Gln
645 650 655

Val Thr Gln Ala Ser Leu Arg Ser His Ile Gly Val Val Pro Gln Asp
660 665 670

15 Thr Val Leu Phe Asn Asp Thr Ile Ala Asp Asn Ile Arg Tyr Gly Arg
675 680 685

20 Val Thr Ala Gly Asn Asp Glu Val Glu Ala Ala Ala Gln Ala Ala Gly
690 695 700

Ile His Asp Ala Ile Met Ala Phe Pro Glu Gly Tyr Arg Thr Gln Val
705 710 715 720

25 Gly Glu Arg Gly Leu Lys Leu Ser Gly Gly Glu Lys Gln Arg Val Ala
725 730 735

30 Ile Ala Arg Thr Ile Leu Lys Ala Pro Gly Ile Ile Leu Leu Asp Glu
740 745 750

Ala Thr Ser Ala Leu Asp Thr Ser Asn Glu Arg Ala Ile Gln Ala Ser
755 760 765

35 Leu Ala Lys Val Cys Ala Asn Arg Thr Thr Ile Val Val Ala His Arg
770 775 780

40 Leu Ser Thr Val Val Asn Ala Asp Gln Ile Leu Val Ile Lys Asp Gly
785 790 795 800

45 Cys Ile Val Glu Arg Gly Arg His Glu Ala Leu Leu Ser Arg Gly Gly
805 810 815

Val Tyr Ala Asp Met Trp Gln Leu Gln Gln Gly Gln Glu Glu Thr Ser
820 825 830

50 Glu Asp Thr Lys Pro Gln Thr Met Glu Arg
835 840

55 <210> 55

EP 1 217 066 A1

<211> 752

<212> PRT

<213> Homo sapiens

5

<400> 55

Met Ala Leu Leu Ala Met His Ser Trp Arg Trp Ala Ala Ala Ala
1 5 10 15

10

Ala Phe Glu Lys Arg Arg His Ser Ala Ile Leu Ile Arg Pro Leu Val
20 25 30

15

Ser Val Ser Gly Ser Gly Pro Gln Trp Arg Pro His Gln Leu Gly Ala
35 40 45

20

Leu Gly Thr Ala Arg Ala Tyr Gln Ile Pro Glu Ser Leu Lys Ser Ile
50 55 60

25

Thr Trp Gln Arg Leu Gly Lys Gly Asn Ser Gly Gln Phe Leu Asp Ala
65 70 75 80

30

Ala Lys Ala Leu Gln Val Trp Pro Leu Ile Glu Lys Arg Thr Cys Trp
85 90 95

35

His Gly His Ala Gly Gly Leu His Thr Asp Pro Lys Glu Gly Leu
100 105 110

40

Lys Asp Val Asp Thr Arg Lys Ile Ile Lys Ala Met Leu Ser Tyr Val
115 120 125

45

Trp Pro Lys Asp Arg Pro Asp Leu Arg Ala Arg Val Pro Ile Ser Leu
130 135 140

50

Gly Phe Leu Gly Gly Ala Lys Ala Met Asn Ile Val Val Pro Phe Met
145 150 155 160

55

Phe Lys Tyr Ala Val Asp Ser Leu Asn Gln Met Ser Gly Asn Met Leu
165 170 175

60

Asn Leu Ser Asp Ala Pro Asn Thr Val Ala Thr Met Ala Thr Ala Val
180 185 190

65

Leu Ile Gly Tyr Gly Val Ser Arg Ala Gly Ala Ala Phe Phe Asn Glu
195 200 205

70

Val Arg Asn Ala Val Phe Gly Lys Val Ala Gln Asn Ser Ile Arg Arg
210 215 220

75

Ile Ala Lys Asn Val Phe Leu His Leu His Asn Leu Asp Leu Gly Phe

EP 1 217 066 A1

	225	230	235	240
5	His Leu Ser Arg Gln Thr Gly Ala Leu Ser Lys Ala Ile Asp Arg Gly			
	245	250	255	
10	Thr Arg Gly Ile Ser Phe Val Leu Ser Ala Leu Val Phe Asn Pro Leu			
	260	265	270	
15	Pro Asn His Val Glu Val Met Leu Leu Val Ser Gly Val Leu Tyr Tyr			
	275	280	285	
20	Lys Cys Cys Ala Gln Leu Leu Gly Asn Leu Gly Thr Leu Gly Thr Tyr			
	290	295	300	
25	Thr Ala Phe Thr Val Ala Val Thr Arg Trp Arg Thr Arg Phe Arg Leu			
	305	310	315	320
	Glu Ile Asp Gln Ala Asp Asn Asp Ala Gly Asn Ala Ala Ile Asp Ser			
	325	330	335	
30	Leu Leu Asn Tyr Glu Thr Val Lys Tyr Phe Asn Asn Glu Arg Tyr Glu			
	340	345	350	
35	Ala Gln Arg Tyr Asp Gly Phe Leu Lys Thr Tyr Glu Thr Ala Ser Leu			
	355	360	365	
	Lys Ser Thr Ser Thr Leu Ala Met Leu Asn Phe Gly Gln Ser Ala Ile			
	370	375	380	
40	Phe Ser Val Gly Leu Thr Ala Ile Met Val Leu Ala Ser Gln Gly Ile			
	385	390	395	400
	Val Ala Gly Thr Leu Thr Val Gly Asp Leu Val Met Val Asn Gly Leu			
	405	410	415	
	Leu Phe Gln Leu Ser Leu Pro Leu Asn Phe Leu Gly Thr Val Tyr Arg			
	420	425	430	
45	Glu Thr Arg Gln Ala Leu Ile Asp Met Asn Thr Leu Phe Thr Leu Leu			
	435	440	445	
50	Lys Val Asp Thr Gln Ile Lys Asp Lys Val Met Ala Ser Pro Leu Gln			
	450	455	460	
55	Ile Thr Pro Gln Thr Ala Thr Val Ala Phe Asp Asn Val His Phe Glu			
	465	470	475	480
	Tyr Ile Glu Gly Gln Lys Val Leu Ser Gly Ile Ser Phe Glu Val Pro			

EP 1 217 066 A1

	485	490	495
5	Ala Gly Lys Lys Val Ala Ile Val Gly Gly Ser Gly Ser Gly Lys Ser 500	505	510
10	Thr Ile Val Arg Leu Leu Phe Arg Phe Tyr Glu Pro Gln Lys Gly Ser 515	520	525
15	Ile Tyr Leu Ala Gly Gln Asn Ile Gln Asp Val Ser Leu Glu Ser Leu 530	535	540
20	Arg Arg Ala Val Gly Val Val Pro Gln Asp Ala Val Leu Phe His Asn 545	550	555
25	Thr Ile Tyr Tyr Asn Leu Leu Tyr Gly Asn Ile Ser Ala Ser Pro Glu 565	570	575
30	Glu Val Tyr Ala Val Ala Lys Leu Ala Gly Leu His Asp Ala Ile Leu 580	585	590
35	Arg Met Pro His Gly Tyr Asp Thr Gln Val Gly Glu Arg Gly Leu Lys 595	600	605
40	Leu Ser Gly Gly Glu Lys Gln Arg Val Ala Ile Ala Arg Ala Ile Leu 610	615	620
45	Lys Asp Pro Pro Val Ile Leu Tyr Asp Glu Ala Thr Ser Ser Leu Asp 625	630	635
50	Ser Ile Thr Glu Glu Thr Ile Leu Gly Ala Met Lys Asp Val Val Lys 645	650	655
55	His Arg Thr Ser Ile Phe Ile Ala His Arg Leu Ser Thr Val Val Asp 660	665	670
	Ala Asp Glu Ile Ile Val Leu Asp Gln Gly Lys Val Ala Glu Arg Gly 675	680	685
	Thr His His Gly Leu Leu Ala Asn Pro His Ser Ile Tyr Ser Glu Met 690	695	700
	Trp His Thr Gln Ser Ser Arg Val Gln Asn His Asp Asn Pro Lys Trp 705	710	715
	Glu Ala Lys Lys Glu Asn Ile Ser Lys Glu Glu Glu Arg Lys Lys Leu 725	730	735
	Gln Glu Glu Ile Val Asn Ser Val Lys Gly Cys Gly Asn Cys Ser Cys		

EP 1 217 066 A1

740

745

750

5

10 <210> 56
 <211> 718
 <212> PRT
 <213> Homo sapiens
 15 <400> 56
 Met Leu Val His Leu Phe Arg Val Gly Ile Arg Gly Gly Pro Phe Pro
 1 5 10 15
 20 Gly Arg Leu Leu Pro Pro Leu Arg Phe Gln Thr Phe Ser Ala Val Arg
 20 25 30
 25 Tyr Ser Asp Gly Tyr Arg Ser Ser Ser Leu Leu Arg Ala Val Ala His
 35 40 45
 30 Leu Arg Ser Gln Leu Trp Ala His Leu Pro Arg Ala Pro Leu Ala Pro
 50 55 60
 35 Arg Trp Ser Pro Ser Ala Trp Cys Trp Val Gly Gly Ala Leu Leu Gly
 65 70 75 80
 35 Pro Met Val Leu Ser Lys His Pro His Leu Cys Leu Val Ala Leu Cys
 85 90 95
 40 Glu Ala Glu Glu Ala Pro Pro Ala Ser Ser Thr Pro His Val Val Gly
 100 105 110
 45 Ser Arg Phe Asn Trp Lys Leu Phe Trp Gln Phe Leu His Pro His Leu
 115 120 125
 45 Leu Val Leu Gly Val Ala Val Val Leu Ala Leu Gly Ala Ala Leu Val
 130 135 140
 50 Asn Val Gln Ile Pro Leu Leu Leu Gly Gln Leu Val Lys Val Val Ala
 145 150 155 160
 55 Lys Tyr Thr Arg Asp His Val Gly Ser Phe Met Thr Glu Ser Gln Asn
 165 170 175
 55 Leu Ser Thr His Leu Leu Ile Leu Tyr Gly Val Gln Gly Leu Leu Thr
 180 185 190

EP 1 217 066 A1

Phe Gly Tyr Leu Val Leu Leu Ser His Val Gly Glu Arg Met Ala Val
 195 200 205
 5 Asp Met Arg Arg Ala Leu Phe Ser Ser Leu Leu Arg Gln Asn Ile Thr
 210 215 220
 10 Phe Phe Asp Ala Asn Lys Thr Gly Gln Leu Val Ser Arg Leu Thr Thr
 225 230 235 240
 15 Asp Val Gln Glu Phe Lys Ser Ser Phe Lys Leu Val Ile Ser Gln Gly
 245 250 255
 Leu Arg Ser Cys Ser Gln Val Ala Gly Cys Leu Val Ser Leu Ser Met
 260 265 270
 20 Leu Ser Thr Arg Leu Thr Leu Leu Leu Met Val Ala Thr Pro Ala Leu
 275 280 285
 25 Met Gly Val Gly Thr Leu Met Gly Ser Gly Leu Arg Lys Leu Ser Arg
 290 295 300
 30 Gln Cys Gln Glu His Ile Ala Arg Ala Met Gly Val Ala Asp Glu Ala
 305 310 315 320
 35 Leu Gly Asn Val Arg Thr Val Arg Ala Leu Ala Met Glu Gln Arg Glu
 325 330 335
 Glu Glu Arg Tyr Gly Ala Glu Leu Glu Ala Cys Arg Cys Arg Ala Glu
 340 345 350
 40 Glu Leu Gly Arg Gly Ile Ala Leu Phe Gln Gly Leu Ser Asn Ile Ala
 355 360 365
 45 Phe Asn Cys Met Val Leu Gly Thr Leu Phe Ile Gly Gly Ser Leu Val
 370 375 380
 Ala Gly Gln Gln Leu Thr Gly Gly Asp Leu Met Ser Phe Leu Val Ala
 385 390 395 400
 50 Ser Gln Thr Val Gln Arg Ser Met Ala Asn Leu Ser Val Leu Phe Gly
 405 410 415
 Gln Val Val Arg Gly Leu Ser Ala Gly Ala Arg Val Phe Glu Tyr Met
 420 425 430
 55 Ala Leu Asn Pro Cys Ile Pro Leu Ser Gly Gly Cys Cys Val Pro Lys
 435 440 445

Glu Gln Leu Arg Gly Ser Val Thr Phe Gln Asn Val Cys Phe Ser Tyr
 450 455 460
 5

Pro Cys Arg Pro Gly Phe Glu Val Leu Lys Asp Phe Thr Leu Thr Leu
 465 470 475 480

10 Pro Pro Gly Lys Ile Val Ala Leu Val Gly Gln Ser Gly Gly Lys
 485 490 495

Thr Thr Val Ala Ser Leu Leu Glu Arg Phe Tyr Asp Pro Thr Ala Gly
 15 500 505 510

Val Val Met Leu Asp Gly Arg Asp Leu Arg Thr Leu Asp Pro Ser Trp
 515 520 525

20 Leu Arg Gly Gln Val Val Gly Phe Ile Ser Gln Glu Pro Val Leu Phe
 530 535 540

25 Gly Thr Thr Ile Met Glu Asn Ile Arg Phe Gly Lys Leu Glu Ala Ser
 545 550 555 560

Asp Glu Glu Val Tyr Thr Ala Ala Arg Glu Ala Asn Ala His Glu Phe
 565 570 575

30 Ile Thr Ser Phe Pro Glu Gly Tyr Asn Thr Val Val Gly Glu Arg Gly
 580 585 590

35 Thr Thr Leu Ser Gly Gly Gln Lys Gln Arg Leu Ala Ile Ala Arg Ala
 595 600 605

Leu Ile Lys Gln Pro Thr Val Leu Ile Leu Asp Glu Ala Thr Ser Ala
 610 615 620

40 Leu Asp Ala Glu Ser Glu Arg Val Val Gln Glu Ala Leu Asp Arg Ala
 625 630 635 640

45 Ser Ala Gly Arg Thr Val Leu Val Ile Ala His Arg Leu Ser Thr Val
 645 650 655

Arg Gly Ala His Cys Ile Val Val Met Ala Asp Gly Arg Val Trp Glu
 660 665 670

50 Ala Gly Thr His Glu Glu Leu Leu Lys Lys Gly Gly Leu Tyr Ala Glu
 675 680 685

55 Leu Ile Arg Arg Gln Ala Leu Asp Ala Pro Arg Thr Ala Ala Pro Pro
 690 695 700

Pro Lys Lys Pro Glu Gly Pro Arg Ser His Gln His Lys Ser
 705 710 715

5

<210> 57
 10 <211> 723
 <212> PRT
 <213> Homo sapiens

<400> 57
 15 Met Arg Leu Trp Lys Ala Val Val Val Thr Leu Ala Phe Met Ser Val
 1 5 10 15

20 Asp Ile Cys Val Thr Thr Ala Ile Tyr Val Phe Ser His Leu Asp Arg
 20 25 30

Ser Leu Leu Glu Asp Ile Arg His Phe Asn Ile Phe Asp Ser Val Leu
 35 40 45

25

Asp Leu Trp Ala Ala Cys Leu Tyr Arg Ser Cys Leu Leu Leu Gly Ala
 50 55 60

30

Thr Ile Gly Val Ala Lys Asn Ser Ala Leu Gly Pro Arg Arg Leu Arg
 65 70 75 80

35

Ala Ser Trp Leu Val Ile Thr Leu Val Cys Leu Phe Val Gly Ile Tyr
 85 90 95

Ala Met Val Lys Leu Leu Phe Ser Glu Val Arg Arg Pro Ile Arg
 100 105 110

40

Asp Pro Trp Phe Trp Ala Leu Phe Val Trp Thr Tyr Ile Ser Leu Gly
 115 120 125

45

Ala Ser Phe Leu Leu Trp Trp Leu Leu Ser Thr Val Arg Pro Gly Thr
 130 135 140

Gln Ala Leu Glu Pro Gly Ala Ala Thr Glu Ala Glu Gly Phe Pro Gly
 145 150 155 160

50

Ser Gly Arg Pro Pro Pro Glu Gln Ala Ser Gly Ala Thr Leu Gln Lys
 165 170 175

55

Leu Leu Ser Tyr Thr Lys Pro Asp Val Ala Phe Leu Val Ala Ala Ser
 180 185 190

EP 1 217 066 A1

Phe Phe Leu Ile Val Ala Ala Leu Gly Glu Thr Phe Leu Pro Tyr Tyr
195 200 205

5 Thr Gly Arg Ala Ile Asp Gly Ile Val Ile Gln Lys Ser Met Asp Gln
210 215 220

10 Phe Ser Thr Ala Val Val Ile Val Cys Leu Leu Ala Ile Gly Ser Ser
225 230 235 240

Phe Ala Ala Gly Ile Arg Gly Gly Ile Phe Thr Leu Ile Phe Ala Arg
245 250 255

15 Leu Asn Ile Arg Leu Arg Asn Cys Leu Phe Arg Ser Leu Val Ser Gln
260 265 270

20 Glu Thr Ser Phe Phe Asp Glu Asn Arg Thr Gly Asp Leu Ile Ser Arg
275 280 285

Leu Thr Ser Asp Thr Thr Met Val Ser Asp Leu Val Ser Gln Asn Ile
290 295 300

25 Asn Val Phe Leu Arg Asn Thr Val Lys Val Thr Gly Val Val Val Phe
305 310 315 320

30 Met Phe Ser Leu Ser Trp Gln Leu Ser Leu Val Thr Phe Met Gly Phe
325 330 335

Pro Ile Ile Met Met Val Ser Asn Ile Tyr Gly Lys Tyr Tyr Lys Arg
340 345 350

35 Leu Ser Lys Glu Val Gln Asn Ala Leu Ala Arg Ala Ser Asn Thr Ala
355 360 365

40 Glu Glu Thr Ile Ser Ala Met Lys Thr Val Arg Ser Phe Ala Asn Glu
370 375 380

Glu Glu Glu Ala Glu Val Tyr Leu Arg Lys Leu Gln Gln Val Tyr Lys
45 385 390 395 400

Leu Asn Arg Lys Glu Ala Ala Ala Tyr Met Tyr Tyr Val Trp Gly Ser
405 410 415

50 Gly Ser Val Gly Ser Val Tyr Ser Gly Leu Met Gln Gly Val Gly Ala
420 425 430

Ala Glu Lys Val Phe Glu Phe Ile Asp Arg Gln Pro Thr Met Val His
55 435 440 445

EP 1 217 066 A1

Asp Gly Ser Leu Ala Pro Asp His Leu Glu Gly Arg Val Asp Phe Glu
450 455 460

5 Asn Val Thr Phe Thr Tyr Arg Thr Arg Pro His Thr Gln Val Leu Gln
465 470 475 480

Asn Val Ser Phe Ser Leu Ser Pro Gly Lys Val Thr Ala Leu Val Gly
10 485 490 495

Pro Ser Gly Ser Gly Lys Ser Ser Cys Val Asn Ile Leu Glu Asn Phe
500 505 510

15 Tyr Pro Leu Glu Gly Arg Val Leu Leu Asp Gly Lys Pro Ile Ser
515 520 525

Ala Tyr Asp His Lys Tyr Leu His Arg Val Ile Ser Leu Val Ser Gln
20 530 535 540

Glu Pro Val Leu Phe Ala Arg Ser Ile Thr Asp Asn Ile Ser Tyr Gly
545 550 555 560

25 Leu Pro Thr Val Pro Phe Glu Met Val Val Glu Ala Ala Gln Lys Ala
565 570 575

Asn Ala His Gly Phe Ile Met Glu Leu Gln Asp Gly Tyr Ser Thr Glu
30 580 585 590

Thr Gly Glu Lys Gly Ala Gln Leu Ser Gly Gly Gln Lys Gln Arg Val
595 600 605

35 Ala Met Ala Arg Ala Leu Val Arg Asn Pro Pro Val Leu Ile Leu Asp
610 615 620

Glu Ala Thr Ser Ala Leu Asp Ala Glu Ser Glu Tyr Leu Ile Gln Gln
40 625 630 635 640

Ala Ile His Gly Asn Leu Gln Lys His Thr Val Leu Ile Ile Ala His
45 645 650 655

Arg Leu Ser Thr Val Glu His Ala His Leu Ile Val Val Leu Asp Lys
660 665 670

50 Gly Arg Val Val Gln Gln Gly Thr His Gln Gln Leu Leu Ala Gln Gly
675 680 685

Gly Leu Tyr Ala Lys Leu Val Gln Arg Gln Met Leu Gly Leu Gln Pro
55 690 695 700

EP 1 217 066 A1

Ala Ala Asp Phe Thr Ala Gly His Asn Glu Pro Val Ala Asn Gly Ser
705 710 715 720

5 His Lys Ala

10 <210> 58
<211> 738

<212> PRT
<213> Homo sapiens

15 <400> 58
Met Arg Gly Pro Pro Ala Trp Pro Leu Arg Leu Leu Glu Pro Pro Ser
1 5 10 15

20 Pro Ala Glu Pro Gly Arg Leu Leu Pro Val Ala Cys Val Trp Ala Ala
20 25 30

25 Ala Ser Arg Val Pro Gly Ser Leu Ser Pro Phe Thr Gly Leu Arg Pro
35 40 45

30 Ala Arg Leu Trp Gly Ala Gly Pro Ala Leu Leu Trp Gly Val Gly Ala
50 55 60

35 Ala Arg Arg Trp Arg Ser Gly Cys Arg Gly Gly Pro Gly Ala Ser
65 70 75 80

40 Arg Gly Val Leu Gly Leu Ala Arg Leu Leu Gly Leu Trp Ala Arg Gly
85 90 95

45 Pro Gly Ser Cys Arg Cys Gly Ala Phe Ala Gly Pro Gly Ala Pro Arg
100 105 110

Leu Pro Arg Ala Arg Phe Pro Gly Gly Pro Ala Ala Ala Ala Trp Ala
115 120 125

50 Gly Asp Glu Ala Trp Arg Arg Gly Pro Ala Ala Pro Pro Gly Asp Lys
130 135 140

Gly Arg Leu Arg Pro Ala Ala Ala Gly Leu Pro Glu Ala Arg Lys Leu
145 150 155 160

55 Leu Gly Leu Ala Tyr Pro Glu Arg Arg Arg Leu Ala Ala Ala Val Gly
165 170 175

Phe Leu Thr Met Ser Ser Val Ile Ser Met Ser Ala Pro Phe Phe Leu

EP 1 217 066 A1

	180	185	190
5	Gly Lys Ile Ile Asp Val Ile Tyr Thr Asn Pro Thr Val Asp Tyr Ser 195	200	205
10	Asp Asn Leu Thr Arg Leu Cys Leu Gly Leu Ser Ala Val Phe Leu Cys 210	215	220
15	Gly Ala Ala Ala Asn Ala Ile Arg Val Tyr Leu Met Gln Thr Ser Gly 225	230	235
20	Gln Arg Ile Val Asn Arg Leu Arg Thr Ser Leu Phe Ser Ser Ile Leu 245	250	255
25	Arg Gln Glu Val Ala Phe Phe Asp Lys Thr Arg Thr Gly Glu Leu Ile 260	265	270
30	Asn Arg Leu Ser Ser Asp Thr Ala Leu Leu Gly Arg Ser Val Thr Glu 275	280	285
35	Asn Leu Ser Asp Gly Leu Arg Ala Gly Ala Gln Ala Ser Val Gly Ile 290	295	300
40	Ser Met Met Phe Phe Val Ser Pro Asn Leu Ala Thr Phe Val Leu Ser 305	310	315
45	Val Val Pro Pro Val Ser Ile Ile Ala Val Ile Tyr Gly Arg Tyr Leu 325	330	335
50	Arg Lys Leu Thr Lys Val Thr Gln Asp Ser Leu Ala Gln Ala Thr Gln 340	345	350
55	Leu Ala Glu Glu Arg Ile Gly Asn Val Arg Thr Val Arg Ala Phe Gly 355	360	365
	Lys Glu Met Thr Glu Ile Glu Lys Tyr Ala Ser Lys Val Asp His Val 370	375	380
	Met Gln Leu Ala Arg Lys Glu Ala Val Ala Arg Ala Gly Phe Phe Gly 385	390	395
	Ala Thr Gly Leu Ser Gly Asn Leu Ile Val Leu Ser Val Leu Tyr Lys 405	410	415
	Gly Gly Leu Leu Met Gly Ser Ala His Met Thr Val Gly Glu Leu Ser 420	425	430
	Ser Phe Leu Met Tyr Ala Phe Trp Val Gly Ile Ser Ile Gly Gly Leu		

EP 1 217 066 A1

	435	440	445
5	Ser Ser Phe Tyr Ser Glu Leu Met Lys Gly Leu Gly Ala Gly Gly Arg		
	450	455	460
	Leu Trp Glu Leu Leu Glu Arg Glu Pro Lys Leu Pro Phe Asn Glu Gly		
	465	470	475
10	Val Ile Leu Asn Glu Lys Ser Phe Gln Gly Ala Leu Glu Phe Lys Asn		
	485	490	495
15	Val His Phe Ala Tyr Pro Ala Arg Pro Glu Val Pro Ile Phe Gln Asp		
	500	505	510
	Phe Ser Leu Ser Ile Pro Ser Gly Ser Val Thr Ala Leu Val Gly Pro		
	515	520	525
20	Ser Gly Ser Gly Lys Ser Thr Val Leu Ser Leu Leu Leu Arg Leu Tyr		
	530	535	540
25	Asn Pro Ala Ser Gly Thr Ile Ser Leu Asp Gly His Asp Ile Arg Gln		
	545	550	555
	Leu Asn Pro Val Trp Leu Arg Ser Lys Ile Gly Thr Val Ser Gln Glu		
30	565	570	575
	Pro Ile Leu Phe Ser Cys Ser Ile Ala Glu Asn Ile Ala Tyr Gly Ala		
	580	585	590
35	Asp Asp Pro Ser Ser Val Thr Ala Glu Glu Ile Gln Arg Val Ala Glu		
	595	600	605
	Val Ala Asn Ala Val Ala Phe Ile Arg Asn Phe Pro Gln Gly Phe Asn		
40	610	615	620
	Thr Val Val Gly Glu Lys Gly Val Leu Leu Ser Gly Gly Gln Lys Gln		
	625	630	635
45	Arg Ile Ala Ile Ala Arg Ala Leu Leu Lys Asn Pro Lys Ile Leu Leu		
	645	650	655
	Leu Asp Glu Ala Thr Ser Ala Leu Asp Ala Glu Asn Glu Tyr Leu Val		
50	660	665	670
	Gln Glu Ala Leu Asp Arg Leu Met Asp Gly Arg Thr Val Leu Val Ile		
	675	680	685
55	Ala His Arg Leu Ser Thr Ile Lys Asn Ala Asn Met Val Ala Val Leu		

EP 1 217 066 A1

690

695

700

5 Asp Gln Gly Lys Ile Thr Glu Tyr Gly Lys His Glu Glu Leu Leu Ser
705 710 715 720

10 Lys Pro Asn Gly Ile Tyr Arg Lys Leu Met Asn Lys Gln Ser Phe Ile
725 730 735

Ser Ala

15

<210> 59

<211> 1321

<212> PRT

20 <213> Homo sapiens

<400> 59

25 Met Ser Asp Ser Val Ile Leu Arg Ser Ile Lys Lys Phe Gly Glu Glu
1 5 10 15

Asn Asp Gly Phe Glu Ser Asp Lys Ser Tyr Asn Asn Asp Lys Lys Ser
20 25 30

30 Arg Leu Gln Asp Glu Lys Lys Gly Asp Gly Val Arg Val Gly Phe Phe
35 40 45

35 Gln Leu Phe Arg Phe Ser Ser Ser Thr Asp Ile Trp Leu Met Phe Val
50 55 60

Gly Ser Leu Cys Ala Phe Leu His Gly Ile Ala Gln Pro Gly Val Leu
65 70 75 80

40

Leu Ile Phe Gly Thr Met Thr Asp Val Phe Ile Asp Tyr Asp Val Glu
85 90 95

45

Leu Gln Glu Leu Gln Ile Pro Gly Lys Ala Cys Val Asn Asn Thr Ile
100 105 110

50 Val Trp Thr Asn Ser Ser Leu Asn Gln Asn Met Thr Asn Gly Thr Arg
115 120 125

55

Cys Gly Leu Leu Asn Ile Glu Ser Glu Met Ile Lys Phe Ala Ser Tyr
130 135 140

55

Tyr Ala Gly Ile Ala Val Ala Val Leu Ile Thr Gly Tyr Ile Gln Ile
145 150 155 160

EP 1 217 066 A1

Cys Phe Trp Val Ile Ala Ala Ala Arg Gln Ile Gln Lys Met Arg Lys
165 170 175
5
Phe Tyr Phe Arg Arg Ile Met Arg Met Glu Ile Gly Trp Phe Asp Cys
180 185 190
10 Asn Ser Val Gly Glu Leu Asn Thr Arg Phe Ser Asp Asp Ile Asn Lys
195 200 205
Ile Asn Asp Ala Ile Ala Asp Gln Met Ala Leu Phe Ile Gln Arg Met
210 215 220
15 Thr Ser Thr Ile Cys Gly Phe Leu Leu Gly Phe Phe Arg Gly Trp Lys
225 230 235 240
20 Leu Thr Leu Val Ile Ile Ser Val Ser Pro Leu Ile Gly Ile Gly Ala
245 250 255
Ala Thr Ile Gly Leu Ser Val Ser Lys Phe Thr Asp Tyr Glu Leu Lys
260 265 270
25
Ala Tyr Ala Lys Ala Gly Val Val Ala Asp Glu Val Ile Ser Ser Met
275 280 285
30 Arg Thr Val Ala Ala Phe Gly Gly Glu Lys Arg Glu Val Glu Arg Tyr
290 295 300
Glu Lys Asn Leu Val Phe Ala Gln Arg Trp Gly Ile Arg Lys Gly Ile
305 310 315 320
35 Val Met Gly Phe Phe Thr Gly Phe Val Trp Cys Leu Ile Phe Leu Cys
325 330 335
40 Tyr Ala Val Ala Phe Trp Tyr Gly Ser Thr Leu Val Leu Asp Glu Gly
340 345 350
45 Glu Tyr Thr Pro Gly Thr Leu Val Gln Ile Phe Leu Ser Val Ile Val
355 360 365
Gly Ala Leu Asn Leu Gly Asn Ala Ser Pro Cys Leu Glu Ala Phe Ala
370 375 380
50 Thr Gly Arg Ala Ala Ala Thr Ser Ile Phe Glu Thr Ile Asp Arg Lys
385 390 395 400
55 Pro Ile Ile Asp Cys Met Ser Glu Asp Gly Tyr Lys Leu Asp Arg Ile
405 410 415

EP 1 217 066 A1

Lys Gly Glu Ile Glu Phe His Asn Val Thr Phe His Tyr Pro Ser Arg
420 425 430

5 Pro Glu Val Lys Ile Leu Asn Asp Leu Asn Met Val Ile Lys Pro Gly
435 440 445

10 Glu Met Thr Ala Leu Val Gly Pro Ser Gly Ala Gly Lys Ser Thr Ala
450 455 460

15 Leu Gln Leu Ile Gln Arg Phe Tyr Asp Pro Cys Glu Gly Met Val Thr
465 470 475 480

Val Asp Gly His Asp Ile Arg Ser Leu Asn Ile Gln Trp Leu Arg Asp
485 490 495

20 Gln Ile Gly Ile Val Glu Gln Glu Pro Val Leu Phe Ser Thr Thr Ile
500 505 510

25 Ala Glu Asn Ile Arg Tyr Gly Arg Glu Asp Ala Thr Met Glu Asp Ile
515 520 525

Val Gln Ala Ala Lys Glu Ala Asn Ala Tyr Asn Phe Ile Met Asp Leu
530 535 540

30 Pro Gln Gln Phe Asp Thr Leu Val Gly Glu Gly Gly Gln Met Ser
545 550 555 560

35 Gly Gly Gln Lys Gln Arg Val Ala Ile Ala Arg Ala Leu Ile Arg Asn
565 570 575

Pro Lys Ile Leu Leu Asp Met Ala Thr Ser Ala Leu Asp Asn Glu
580 585 590

40 Ser Glu Ala Met Val Gln Glu Val Leu Ser Lys Ile Gln His Gly His
595 600 605

45 Thr Ile Ile Ser Val Ala His Arg Leu Ser Thr Val Arg Ala Ala Asp
610 615 620

50 Thr Ile Ile Gly Phe Glu His Gly Thr Ala Val Glu Arg Gly Thr His
625 630 635 640

Glu Glu Leu Leu Glu Arg Lys Gly Val Tyr Phe Thr Leu Val Thr Leu
645 650 655

55 Gln Ser Gln Gly Asn Gln Ala Leu Asn Glu Glu Asp Ile Lys Asp Ala
660 665 670

EP 1 217 066 A1

Thr Glu Asp Asp Met Leu Ala Arg Thr Phe Ser Arg Gly Ser Tyr Gln
675 680 685
5 Asp Ser Leu Arg Ala Ser Ile Arg Gln Arg Ser Lys Ser Gln Leu Ser
690 695 700
10 Tyr Leu Val His Glu Pro Pro Leu Ala Val Val Asp His Lys Ser Thr
705 710 715 720
Tyr Glu Glu Asp Arg Lys Asp Lys Asp Ile Pro Val Gln Glu Glu Val
15 725 730 735
Glu Pro Ala Pro Val Arg Arg Ile Leu Lys Phe Ser Ala Pro Glu Trp
740 745 750
20 Pro Tyr Met Leu Val Gly Ser Val Gly Ala Ala Val Asn Gly Thr Val
755 760 765
Thr Pro Leu Tyr Ala Phe Leu Phe Ser Gln Ile Leu Gly Thr Phe Ser
25 770 775 780
Ile Pro Asp Lys Glu Glu Gln Arg Ser Gln Ile Asn Gly Val Cys Leu
785 790 795 800
30 Leu Phe Val Ala Met Gly Cys Val Ser Leu Phe Thr Gln Phe Leu Gln
805 810 815
Gly Tyr Ala Phe Ala Lys Ser Gly Glu Leu Leu Thr Lys Arg Leu Arg
35 820 825 830
Lys Phe Gly Phe Arg Ala Met Leu Gly Gln Asp Ile Ala Trp Phe Asp
835 840 845
40 Asp Leu Arg Asn Ser Pro Gly Ala Leu Thr Thr Arg Leu Ala Thr Asp
850 855 860
Ala Ser Gln Val Gln Gly Ala Ala Gly Ser Gln Ile Gly Met Ile Val
45 865 870 875 880
Asn Ser Phe Thr Asn Val Thr Val Ala Met Ile Ile Ala Phe Ser Phe
885 890 895
50 Ser Trp Lys Leu Ser Leu Val Ile Leu Cys Phe Phe Pro Phe Leu Ala
900 905 910
Leu Ser Gly Ala Thr Gln Thr Arg Met Leu Thr Gly Phe Ala Ser Arg
55 915 920 925

EP 1 217 066 A1

Asp Lys Gln Ala Leu Glu Met Val Gly Gln Ile Thr Asn Glu Ala Leu
930 935 940

5

Ser Asn Ile Arg Thr Val Ala Gly Ile Gly Lys Glu Arg Arg Phe Ile
945 950 955 960

10 Glu Ala Leu Glu Thr Glu Leu Glu Lys Pro Phe Lys Thr Ala Ile Gln
965 970 975

Lys Ala Asn Ile Tyr Gly Phe Cys Phe Ala Phe Ala Gln Cys Ile Met
15 980 985 990

Phe Ile Ala Asn Ser Ala Ser Tyr Arg Tyr Gly Gly Tyr Leu Ile Ser
995 1000 1005

20 Asn Glu Gly Leu His Phe Ser Tyr Val Phe Arg Val Ile Ser Ala Val
1010 1015 1020

Val Leu Ser Ala Thr Ala Leu Gly Arg Ala Phe Ser Tyr Thr Pro Ser
25 1025 1030 1035 1040

Tyr Ala Lys Ala Lys Ile Ser Ala Ala Arg Phe Phe Gln Leu Leu Asp
1045 1050 1055

30 Arg Gln Pro Pro Ile Ser Val Tyr Asn Thr Ala Gly Glu Lys Trp Asp
1060 1065 1070

Asn Phe Gln Gly Lys Ile Asp Phe Val Asp Cys Lys Phe Thr Tyr Pro
35 1075 1080 1085

Ser Arg Pro Asp Ser Gln Val Leu Asn Gly Leu Ser Val Ser Ile Ser
1090 1095 1100

40 Pro Gly Gln Thr Leu Ala Phe Val Gly Ser Ser Gly Cys Gly Lys Ser
1105 1110 1115 1120

45 Thr Ser Ile Gln Leu Leu Glu Arg Phe Tyr Asp Pro Asp Gln Gly Lys
1125 1130 1135

Val Met Ile Asp Gly His Asp Ser Lys Lys Val Asn Val Gln Phe Leu
1140 1145 1150

50 Arg Ser Asn Ile Gly Ile Val Ser Gln Glu Pro Val Leu Phe Ala Cys
1155 1160 1165

55 Ser Ile Met Asp Asn Ile Lys Tyr Gly Asp Asn Thr Lys Glu Ile Pro
1170 1175 1180

EP 1 217 066 A1

Met Glu Arg Val Ile Ala Ala Ala Lys Gln Ala Gln Leu His Asp Phe
1185 1190 1195 1200

5 Val Met Ser Leu Pro Glu Lys Tyr Glu Thr Asn Val Gly Ser Gln Gly
1205 1210 1215

10 Ser Gln Leu Ser Arg Gly Glu Lys Gln Arg Ile Ala Ile Ala Arg Ala
1220 1225 1230

15 Ile Val Arg Asp Pro Lys Ile Leu Leu Asp Glu Ala Thr Ser Ala
1235 1240 1245

Leu Asp Thr Glu Ser Glu Lys Thr Val Gln Val Ala Leu Asp Lys Ala
1250 1255 1260

20 Arg Glu Gly Arg Thr Cys Ile Val Ile Ala His Arg Leu Ser Thr Ile
1265 1270 1275 1280

25 Gln Asn Ala Asp Ile Ile Ala Val Met Ala Gln Gly Val Val Ile Glu
1285 1290 1295

Lys Gly Thr His Glu Glu Leu Met Ala Gln Lys Gly Ala Tyr Tyr Lys
1300 1305 1310

30 Leu Val Thr Thr Gly Ser Pro Ile Ser
1315 1320

35 <210> 60
<211> 1481
<212> PRT
40 <213> Homo sapiens

45 <400> 60
Met Ala Leu Arg Gly Phe Cys Ser Ala Asp Gly Ser Asp Pro Leu Trp
1 5 10 15

Asp Trp Asn Val Thr Trp Asn Thr Ser Asn Pro Asp Phe Thr Lys Cys
20 25 30

50 Phe Gln Asn Thr Val Leu Val Trp Val Pro Cys Phe Tyr Leu Trp Ala
35 40 45

Cys Phe Pro Phe Tyr Phe Leu Tyr Leu Ser Arg His Asp Arg Gly Tyr
50 55 60

55

EP 1 217 066 A1

Ile Gln Met Thr Pro Leu Asn Lys Thr Lys Thr Ala Leu Gly Phe Leu
65 70 75 80

5 Leu Trp Ile Val Cys Trp Ala Asp Leu Phe Tyr Ser Phe Trp Glu Arg
85 90 95

10 Ser Arg Gly Ile Phe Leu Ala Pro Val Phe Leu Val Ser Pro Thr Leu
100 105 110

Leu Gly Ile Thr Thr Leu Leu Ala Thr Phe Leu Ile Gln Leu Glu Arg
115 120 125

15 Arg Lys Gly Val Gln Ser Ser Gly Ile Met Leu Thr Phe Trp Leu Val
130 135 140

20 Ala Leu Val Cys Ala Leu Ala Ile Leu Arg Ser Lys Ile Met Thr Ala
145 150 155 160

Leu Lys Glu Asp Ala Gln Val Asp Leu Phe Arg Asp Ile Thr Phe Tyr
165 170 175

25 Val Tyr Phe Ser Leu Leu Leu Ile Gln Leu Val Leu Ser Cys Phe Ser
180 185 190

30 Asp Arg Ser Pro Leu Phe Ser Glu Thr Ile His Asp Pro Asn Pro Cys
195 200 205

Pro Glu Ser Ser Ala Ser Phe Leu Ser Arg Ile Thr Phe Trp Trp Ile
210 215 220

35 Thr Gly Leu Ile Val Arg Gly Tyr Arg Gln Pro Leu Glu Gly Ser Asp
225 230 235 240

40 Leu Trp Ser Leu Asn Lys Glu Asp Thr Ser Glu Gln Val Val Pro Val
245 250 255

Leu Val Lys Asn Trp Lys Lys Glu Cys Ala Lys Thr Arg Lys Gln Pro
45 260 265 270

Val Lys Val Val Tyr Ser Ser Lys Asp Pro Ala Gln Pro Lys Glu Ser
275 280 285

50 Ser Lys Val Asp Ala Asn Glu Glu Val Glu Ala Leu Ile Val Lys Ser
290 295 300

Pro Gln Lys Glu Trp Asn Pro Ser Leu Phe Lys Val Leu Tyr Lys Thr
55 305 310 315 320

EP 1 217 066 A1

Phe Gly Pro Tyr Phe Leu Met Ser Phe Phe Phe Lys Ala Ile His Asp
325 330 335

5 Leu Met Met Phe Ser Gly Pro Gln Ile Leu Lys Leu Leu Ile Lys Phe
340 345 350

10 Val Asn Asp Thr Lys Ala Pro Asp Trp Gln Gly Tyr Phe Tyr Thr Val
355 360 365

Leu Leu Phe Val Thr Ala Cys Leu Gln Thr Leu Val Leu His Gln Tyr
370 375 380

15 Phe His Ile Cys Phe Val Ser Gly Met Arg Ile Lys Thr Ala Val Ile
385 390 395 400

20 Gly Ala Val Tyr Arg Lys Ala Leu Val Ile Thr Asn Ser Ala Arg Lys
405 410 415

Ser Ser Thr Val Gly Glu Ile Val Asn Leu Met Ser Val Asp Ala Gln
420 425 430

25 Arg Phe Met Asp Leu Ala Thr Tyr Ile Asn Met Ile Trp Ser Ala Pro
435 440 445

Leu Gln Val Ile Leu Ala Leu Tyr Leu Leu Trp Leu Asn Leu Gly Pro
450 455 460

30 Ser Val Leu Ala Gly Val Ala Val Met Val Leu Met Val Pro Val Asn
465 470 475 480

35 Ala Val Met Ala Met Lys Thr Lys Thr Tyr Gln Val Ala His Met Lys
485 490 495

40 Ser Lys Asp Asn Arg Ile Lys Leu Met Asn Glu Ile Leu Asn Gly Ile
500 505 510

Lys Val Leu Lys Leu Tyr Ala Trp Glu Leu Ala Phe Lys Asp Lys Val
515 520 525

45 Leu Ala Ile Arg Gln Glu Glu Leu Lys Val Leu Lys Lys Ser Ala Tyr
530 535 540

50 Leu Ser Ala Val Gly Thr Phe Thr Trp Val Cys Thr Pro Phe Leu Ala
545 550 555 560

55 Ser Val Ser Leu Lys Arg Leu Arg Ile Phe Leu Ser His Glu Glu Leu
565 570 575

EP 1 217 066 A1

Glu Pro Asp Ser Ile Glu Arg Arg Pro Val Lys Asp Gly Gly Gly Thr
580 585 590

5 Asn Ser Ile Thr Val Arg Asn Ala Thr Phe Thr Trp Ala Arg Ser Asp
595 600 605

10 Pro Pro Thr Leu Asn Gly Ile Thr Phe Ser Ile Pro Glu Gly Ala Leu
610 615 620

Val Ala Val Val Gly Gln Val Gly Cys Gly Lys Ser Ser Leu Leu Ser
625 630 635 640

15 Ala Leu Leu Ala Glu Met Asp Lys Val Glu Gly His Val Ala Ile Lys
645 650 655

20 Gly Ser Val Ala Tyr Val Pro Gln Gln Ala Trp Ile Gln Asn Asp Ser
660 665 670

Leu Arg Glu Asn Ile Leu Phe Gly Cys Gln Leu Glu Glu Pro Tyr Tyr
675 680 685

25 Arg Ser Val Ile Gln Ala Cys Ala Leu Leu Pro Asp Leu Glu Ile Leu
690 695 700

30 Pro Ser Gly Asp Arg Thr Glu Ile Gly Glu Lys Gly Val Asn Leu Ser
705 710 715 720

Gly Gly Gln Lys Gln Arg Val Ser Leu Ala Arg Ala Val Tyr Ser Asn
725 730 735

35 Ala Asp Ile Tyr Leu Phe Asp Asp Pro Leu Ser Ala Val Asp Ala His
740 745 750

40 Val Gly Lys His Ile Phe Glu Asn Val Ile Gly Pro Lys Gly Met Leu
755 760 765

Lys Asn Lys Thr Arg Ile Leu Val Thr His Ser Met Ser Tyr Leu Pro
770 775 780

45 Gln Val Asp Val Ile Ile Val Met Ser Gly Gly Lys Ile Ser Glu Met
785 790 795 800

50 Gly Ser Tyr Gln Glu Leu Leu Ala Arg Asp Gly Ala Phe Ala Glu Phe
805 810 815

Leu Arg Thr Tyr Ala Ser Thr Glu Gln Glu Gln Asp Ala Glu Glu Asn
820 825 830

EP 1 217 066 A1

Gly Val Thr Gly Val Ser Gly Pro Gly Lys Glu Ala Lys Gln Met Glu
835 840 845

5 Asn Gly Met Leu Val Thr Asp Ser Ala Gly Lys Gln Leu Gln Arg Gln
850 855 860

Leu Ser Ser Ser Ser Tyr Ser Gly Asp Ile Ser Arg His His Asn
10 865 870 875 880

Ser Thr Ala Glu Leu Gln Lys Ala Glu Ala Lys Lys Glu Glu Thr Trp
885 890 895

15 Lys Leu Met Glu Ala Asp Lys Ala Gln Thr Gly Gln Val Lys Leu Ser
900 905 910

Val Tyr Trp Asp Tyr Met Lys Ala Ile Gly Leu Phe Ile Ser Phe Leu
20 915 920 925

Ser Ile Phe Leu Phe Met Cys Asn His Val Ser Ala Leu Ala Ser Asn
930 935 940

25 Tyr Trp Leu Ser Leu Trp Thr Asp Asp Pro Ile Val Asn Gly Thr Gln
945 950 955 960

Glu His Thr Lys Val Arg Leu Ser Val Tyr Gly Ala Leu Gly Ile Ser
30 965 970 975

Gln Gly Ile Ala Val Phe Gly Tyr Ser Met Ala Val Ser Ile Gly Gly
980 985 990

35 Ile Leu Ala Ser Arg Cys Leu His Val Asp Leu Leu His Ser Ile Leu
995 1000 1005

Arg Ser Pro Met Ser Phe Phe Glu Arg Thr Pro Ser Gly Asn Leu Val
40 1010 1015 1020

Asn Arg Phe Ser Lys Glu Leu Asp Thr Val Asp Ser Met Ile Pro Glu
45 1025 1030 1035 1040

Val Ile Lys Met Phe Met Gly Ser Leu Phe Asn Val Ile Gly Ala Cys
1045 1050 1055

Ile Val Ile Leu Leu Ala Thr Pro Ile Ala Ala Ile Ile Ile Pro Pro
50 1060 1065 1070

Leu Gly Leu Ile Tyr Phe Phe Val Gln Arg Phe Tyr Val Ala Ser Ser
55 1075 1080 1085

EP 1 217 066 A1

Arg Gln Leu Lys Arg Leu Glu Ser Val Ser Arg Ser Pro Val Tyr Ser
 1090 1095 1100
 5 His Phe Asn Glu Thr Leu Leu Gly Val Ser Val Ile Arg Ala Phe Glu
 1105 1110 1115 1120
 10 Glu Gln Glu Arg Phe Ile His Gln Ser Asp Leu Lys Val Asp Glu Asn
 1125 1130 1135
 15 Gln Lys Ala Tyr Tyr Pro Ser Ile Val Ala Asn Arg Trp Leu Ala Val
 1140 1145 1150
 20 Arg Leu Glu Cys Val Gly Asn Cys Ile Val Leu Phe Ala Ala Leu Phe
 1155 1160 1165
 25 Ala Val Ile Ser Arg His Ser Leu Ser Ala Gly Leu Val Gly Leu Ser
 1170 1175 1180
 30 Val Ser Tyr Ser Leu Gln Val Thr Thr Tyr Leu Asn Trp Leu Val Arg
 1185 1190 1195 1200
 35 Met Ser Ser Glu Met Glu Thr Asn Ile Val Ala Val Glu Arg Leu Lys
 1205 1210 1215
 40 Glu Tyr Ser Glu Thr Glu Lys Glu Ala Pro Trp Gln Ile Gln Glu Thr
 1220 1225 1230
 45 Ala Pro Pro Ser Ser Trp Pro Gln Val Gly Arg Val Glu Phe Arg Asn
 1235 1240 1245
 50 Tyr Cys Leu Arg Tyr Arg Glu Asp Leu Asp Phe Val Leu Arg His Ile
 1250 1255 1260
 55 Asn Val Thr Ile Asn Gly Gly Glu Lys Val Gly Ile Val Gly Thr Gly
 1265 1270 1275 1280
 Ala Gly Lys Ser Ser Leu Thr Leu Gly Leu Phe Arg Ile Asn Glu Ser
 1285 1290 1295
 Ala Glu Gly Glu Ile Ile Asp Gly Ile Asn Ile Ala Lys Ile Gly
 1300 1305 1310
 60 Leu His Asp Leu Arg Phe Lys Ile Thr Ile Ile Pro Gln Asp Pro Val
 1315 1320 1325
 65 Leu Phe Ser Gly Ser Leu Arg Met Asn Leu Asp Pro Phe Ser Gln Tyr
 1330 1335 1340

EP 1 217 066 A1

Ser Asp Glu Glu Val Trp Thr Ser Leu Glu Leu Ala His Leu Lys Asp
1345 1350 1355 1360

5 Phe Val Ser Ala Leu Pro Asp Lys Leu Asp His Glu Cys Ala Glu Gly
1365 1370 1375

Gly Glu Asn Leu Ser Val Gly Gln Arg Gln Leu Val Cys Leu Ala Arg
10 1380 1385 1390

Ala Leu Leu Arg Lys Thr Lys Ile Leu Val Leu Asp Glu Ala Thr Ala
1395 1400 1405

15 Ala Val Asp Leu Glu Thr Asp Asp Leu Ile Gln Ser Thr Ile Arg Thr
1410 1415 1420

Gln Phe Glu Asp Cys Thr Val Leu Thr Ile Ala His Arg Leu Asn Thr
20 1425 1430 1435 1440

Ile Met Asp Tyr Thr Arg Val Ile Val Leu Asp Lys Gly Glu Ile Gln
1445 1450 1455

25 Glu Tyr Gly Ala Pro Ser Asp Leu Leu Gln Gln Arg Gly Leu Phe Tyr
1460 1465 1470

30 Ser Met Ala Lys Asp Ala Gly Leu Val
1475 1480

35 <210> 61
<211> 1545
<212> PRT
<213> Homo sapiens

40 <400> 61
Met Leu Glu Lys Phe Cys Asn Ser Thr Phe Trp Asn Ser Ser Phe Leu
1 5 10 15

45 Asp Ser Pro Glu Ala Asp Leu Pro Leu Cys Phe Glu Gln Thr Val Leu
20 25 30

50 Val Trp Ile Pro Leu Gly Phe Leu Trp Leu Leu Ala Pro Trp Gln Leu
35 40 45

Leu His Val Tyr Lys Ser Arg Thr Lys Arg Ser Ser Thr Thr Lys Leu
55 55 60

55 Tyr Leu Ala Lys Gln Val Phe Val Gly Phe Leu Leu Ile Leu Ala Ala

EP 1217066 A1

	65	70	75	80
5	Ile Glu Leu Ala Leu Val Leu Thr Glu Asp Ser Gly Gln Ala Thr Val 85		90	95
10	Pro Ala Val Arg Tyr Thr Asn Pro Ser Leu Tyr Leu Gly Thr Trp Leu 100	105		110
15	Leu Val Leu Leu Ile Gln Tyr Ser Arg Gln Trp Cys Val Gln Lys Asn 115	120	125	
20	Ser Trp Phe Leu Ser Leu Phe Trp Ile Leu Ser Ile Leu Cys Gly Thr 130	135	140	
25	Phe Gln Phe Gln Thr Leu Ile Arg Thr Leu Leu Gln Gly Asp Asn Ser 145	150	155	160
30	Asn Leu Ala Tyr Ser Cys Leu Phe Phe Ile Ser Tyr Gly Phe Gln Ile 165	170	175	
35	Leu Ile Leu Ile Phe Ser Ala Phe Ser Glu Asn Asn Glu Ser Ser Asn 180	185	190	
40	Asn Pro Ser Ser Ile Ala Ser Phe Leu Ser Ser Ile Thr Tyr Ser Trp 195	200	205	
45	Tyr Asp Ser Ile Ile Leu Lys Gly Tyr Lys Arg Pro Leu Thr Leu Glu 210	215	220	
50	Asp Val Trp Glu Val Asp Glu Glu Met Lys Thr Lys Thr Leu Val Ser 225	230	235	240
55	Lys Phe Glu Thr His Met Lys Arg Glu Leu Gln Lys Ala Arg Arg Ala 245	250	255	
	Leu Gln Arg Arg Gln Glu Lys Ser Ser Gln Gln Asn Ser Gly Ala Arg 260	265	270	
	Leu Pro Gly Leu Asn Lys Asn Gln Ser Gln Asp Ala Leu Val 275	280	285	
	Leu Glu Asp Val Glu Lys Lys Lys Lys Ser Gly Thr Lys Lys Asp 290	295	300	
	Val Pro Lys Ser Trp Leu Met Lys Ala Leu Phe Lys Thr Phe Tyr Met 305	310	315	320
	Val Leu Leu Lys Ser Phe Leu Leu Lys Leu Val Asn Asp Ile Phe Thr			

EP 1 217 066 A1

	325	330	335
5	Phe Val Ser Pro Gln Leu Leu Lys Leu Leu Ile Ser Phe Ala Ser Asp 340	345	350
	Arg Asp Thr Tyr Leu Trp Ile Gly Tyr Leu Cys Ala Ile Leu Leu Phe 355	360	365
10	Thr Ala Ala Leu Ile Gln Ser Phe Cys Leu Gln Cys Tyr Phe Gln Leu 370	375	380
15	Cys Phe Lys Leu Gly Val Lys Val Arg Thr Ala Ile Met Ala Ser Val 385	390	395
	Tyr Lys Lys Ala Leu Thr Leu Ser Asn Leu Ala Arg Lys Glu Tyr Thr 405	410	415
20	Val Gly Glu Thr Val Asn Leu Met Ser Val Asp Ala Gln Lys Leu Met 420	425	430
25	Asp Val Thr Asn Phe Met His Met Leu Trp Ser Ser Val Leu Gln Ile 435	440	445
	Val Leu Ser Ile Phe Phe Leu Trp Arg Glu Leu Gly Pro Ser Val Leu 450	455	460
30	Ala Gly Val Gly Val Met Val Leu Val Ile Pro Ile Asn Ala Ile Leu 465	470	475
	Ser Thr Lys Ser Lys Thr Ile Gln Val Lys Asn Met Lys Asn Lys Asp 485	490	495
35	Lys Arg Leu Lys Ile Met Asn Glu Ile Leu Ser Gly Ile Lys Ile Leu 500	505	510
	Lys Tyr Phe Ala Trp Glu Pro Ser Phe Arg Asp Gln Val Gln Asn Leu 515	520	525
40	Arg Lys Lys Glu Leu Lys Asn Leu Leu Ala Phe Ser Gln Leu Gln Cys 530	535	540
	Val Val Ile Phe Val Phe Gln Leu Thr Pro Val Leu Val Ser Val Val 545	550	555
45	Thr Phe Ser Val Tyr Val Leu Val Asp Ser Asn Asn Ile Leu Asp Ala 565	570	575
50	Gln Lys Ala Phe Thr Ser Ile Thr Leu Phe Asn Ile Leu Arg Phe Pro		

EP 1 217 066 A1

	580	585	590
5	Leu Ser Met Leu Pro Met Met Ile Ser Ser Met Leu Gln Ala Ser Val		
	595	600	605
	Ser Thr Glu Arg Leu Glu Lys Tyr Leu Gly Gly Asp Asp Leu Asp Thr		
10	610	615	620
	Ser Ala Ile Arg His Asp Cys Asn Phe Asp Lys Ala Met Gln Phe Ser		
	625	630	635
15	640	Glu Ala Ser Phe Thr Trp Glu His Asp Ser Glu Ala Thr Val Arg Asp	
	645	650	655
20	Val Asn Leu Asp Ile Met Ala Gly Gln Leu Val Ala Val Ile Gly Pro		
	660	665	670
	Val Gly Ser Gly Lys Ser Ser Leu Ile Ser Ala Met Leu Gly Glu Met		
	675	680	685
25	Glu Asn Val His Gly His Ile Thr Ile Lys Gly Thr Thr Ala Tyr Val		
	690	695	700
30	Pro Gln Gln Ser Trp Ile Gln Asn Gly Thr Ile Lys Asp Asn Ile Leu		
	705	710	715
	720	Phe Gly Thr Glu Phe Asn Glu Lys Arg Tyr Gln Gln Val Leu Glu Ala	
	725	730	735
35	Cys Ala Leu Leu Pro Asp Leu Glu Met Leu Pro Gly Gly Asp Leu Ala		
	740	745	750
40	Glu Ile Gly Glu Lys Gly Ile Asn Leu Ser Gly Gly Gln Lys Gln Arg		
	755	760	765
	Ile Ser Leu Ala Arg Ala Thr Tyr Gln Asn Leu Asp Ile Tyr Leu Leu		
	770	775	780
45	Asp Asp Pro Leu Ser Ala Val Asp Ala His Val Gly Lys His Ile Phe		
	785	790	795
	800	Asn Lys Val Leu Gly Pro Asn Gly Leu Leu Lys Gly Lys Thr Arg Leu	
50	805	810	815
	Leu Val Thr His Ser Met His Phe Leu Pro Gln Val Asp Glu Ile Val		
	820	825	830
55	Val Leu Gly Asn Gly Thr Ile Val Glu Lys Gly Ser Tyr Ser Ala Leu		

EP 1 217 066 A1

	835	840	845
5	Leu Ala Lys Lys Gly Glu Phe Ala Lys Asn Leu Lys Thr Phe Leu Arg 850	855	860
10	His Thr Gly Pro Glu Glu Glu Ala Thr Val His Asp Gly Ser Glu Glu 865	870	875
15	Glu Asp Asp Asp Tyr Gly Leu Ile Ser Ser Val Glu Glu Ile Pro Glu 885	890	895
20	Asp Ala Ala Ser Ile Thr Met Arg Arg Glu Asn Ser Phe Arg Arg Thr 900	905	910
25	Leu Ser Arg Ser Ser Arg Ser Asn Gly Arg His Leu Lys Ser Leu Arg 915	920	925
30	Asn Ser Leu Lys Thr Arg Asn Val Asn Ser Leu Lys Glu Asp Glu Glu 930	935	940
35	Leu Val Lys Gly Gln Lys Leu Ile Lys Lys Glu Phe Ile Glu Thr Gly 945	950	955
40	Lys Val Lys Phe Ser Ile Tyr Leu Glu Tyr Leu Gln Ala Ile Gly Leu 965	970	975
45	Phe Ser Ile Phe Phe Ile Ile Leu Ala Phe Val Met Asn Ser Val Ala 980	985	990
50	Phe Ile Gly Ser Asn Leu Trp Leu Ser Ala Trp Thr Ser Asp Ser Lys 995	1000	1005
55	Ile Phe Asn Ser Thr Asp Tyr Pro Ala Ser Gln Arg Asp Met Arg Val 1010	1015	1020
60	Gly Val Tyr Gly Ala Leu Gly Leu Ala Gln Gly Ile Phe Val Phe Ile 1025	1030	1035
65	Ala His Phe Trp Ser Ala Phe Gly Phe Val His Ala Ser Asn Ile Leu 1045	1050	1055
70	His Lys Gln Leu Leu Asn Asn Ile Leu Arg Ala Pro Met Arg Phe Phe 1060	1065	1070
75	Asp Thr Thr Pro Thr Gly Arg Ile Val Asn Arg Phe Ala Gly Asp Ile 1075	1080	1085
80	Ser Thr Val Asp Asp Thr Leu Pro Gln Ser Leu Arg Ser Trp Ile Thr		

EP 1 217 066 A1

	1090	1095	1100
5	Cys Phe Leu Gly Ile Ile Ser Thr Leu Val Met Ile Cys Met Ala Thr		
	1105	1110	1115
	1120		
	Pro Val Phe Thr Ile Ile Val Ile Pro Leu Gly Ile Ile Tyr Val Ser		
10		1125	1130
		1135	
	Val Gln Met Phe Tyr Val Ser Thr Ser Arg Gln Leu Arg Arg Leu Asp		
	1140	1145	1150
15	Ser Val Thr Arg Ser Pro Ile Tyr Ser His Phe Ser Glu Thr Val Ser		
	1155	1160	1165
	Gly Leu Pro Val Ile Arg Ala Phe Glu His Gln Gln Arg Phe Leu Lys		
20	1170	1175	1180
	His Asn Glu Val Arg Ile Asp Thr Asn Gln Lys Cys Val Phe Ser Trp		
	1185	1190	1195
	1200		
25	Ile Thr Ser Asn Arg Trp Leu Ala Ile Arg Leu Glu Leu Val Gly Asn		
	1205	1210	1215
	Leu Thr Val Phe Phe Ser Ala Leu Met Met Val Ile Tyr Arg Asp Thr		
30	1220	1225	1230
	Leu Ser Gly Asp Thr Val Gly Phe Val Leu Ser Asn Ala Leu Asn Ile		
	1235	1240	1245
35	Thr Gln Thr Leu Asn Trp Leu Val Arg Met Thr Ser Glu Ile Glu Thr		
	1250	1255	1260
	Asn Ile Val Ala Val Glu Arg Ile Thr Glu Tyr Thr Lys Val Glu Asn		
40	1265	1270	1275
	1280		
	Glu Ala Pro Trp Val Thr Asp Lys Arg Pro Pro Pro Asp Trp Pro Ser		
	1285	1290	1295
45	Lys Gly Lys Ile Gln Phe Asn Asn Tyr Gln Val Arg Tyr Arg Pro Glu		
	1300	1305	1310
	Leu Asp Leu Val Leu Arg Gly Ile Thr Cys Asp Ile Gly Ser Met Glu		
50	1315	1320	1325
	Leu Lys Ile Gly Val Val Gly Arg Thr Gly Ala Gly Lys Ser Ser Leu Thr		
	1330	1335	1340
55	Asn Cys Leu Phe Arg Ile Leu Glu Ala Ala Gly Gly Gln Ile Ile Ile		

EP 1 217 066 A1

	1345	1350	1355	1360
5	Asp Gly Val Asp Ile Ala Ser Ile Gly Leu His Asp Leu Arg Glu Lys			
	1365	1370	1375	
	Leu Thr Ile Ile Pro Gln Asp Pro Ile Leu Phe Ser Gly Ser Leu Arg			
10	1380	1385	1390	
	Met Asn Leu Asp Pro Phe Asn Asn Tyr Ser Asp Glu Glu Ile Trp Lys			
	1395	1400	1405	
15	Ala Leu Glu Leu Ala His Leu Lys Ser Phe Val Ala Ser Leu Gln Leu			
	1410	1415	1420	
	Gly Leu Ser His Glu Val Thr Glu Ala Gly Gly Asn Leu Ser Ile Gly			
20	1425	1430	1435	1440
	Gln Arg Gln Leu Leu Cys Leu Gly Arg Ala Leu Leu Arg Lys Ser Lys			
	1445	1450	1455	
25	Ile Leu Val Leu Asp Glu Ala Thr Ala Ala Val Asp Leu Glu Thr Asp			
	1460	1465	1470	
	Asn Leu Ile Gln Thr Thr Ile Gln Asn Glu Phe Ala His Cys Thr Val			
30	1475	1480	1485	
	Ile Thr Ile Ala His Arg Leu His Thr Ile Met Asp Ser Asp Lys Val			
	1490	1495	1500	
35	Met Val Leu Asp Asn Gly Lys Ile Ile Glu Cys Gly Ser Pro Glu Glu			
	1505	1510	1515	1520
	Leu Leu Gln Ile Pro Gly Pro Phe Tyr Phe Met Ala Lys Glu Ala Gly			
40	1525	1530	1535	
	Ile Glu Asn Val Asn Ser Thr Lys Phe			
	1540	1545		
45				
	<210> 62			
	<211> 1527			
50	<212> PRT			
	<213> Homo sapiens			
	<400> 62			
55	Met Asp Ala Leu Cys Gly Ser Gly Glu Leu Gly Ser Lys Phe Trp Asp			
	1	5	10	15

EP 1 217 066 A1

Ser Asn Leu Ser Val His Thr Glu Asn Pro Asp Leu Thr Pro Cys Phe
20 25 30

5

Gln Asn Ser Leu Leu Ala Trp Val Pro Cys Ile Tyr Leu Trp Val Ala
35 40 45

10 Leu Pro Cys Tyr Leu Leu Tyr Leu Arg His His Cys Arg Gly Tyr Ile
50 55 60

15 Ile Leu Ser His Leu Ser Lys Leu Lys Met Val Leu Gly Val Leu Leu
65 70 75 80

Trp Cys Val Ser Trp Ala Asp Leu Phe Tyr Ser Phe His Gly Leu Val
85 90 95

20 His Gly Arg Ala Pro Ala Pro Val Phe Phe Val Thr Pro Leu Val Val
100 105 110

25 Gly Val Thr Met Leu Leu Ala Thr Leu Leu Ile Gln Tyr Glu Arg Leu
115 120 125

30 Gln Gly Val Gln Ser Ser Gly Val Leu Ile Ile Phe Trp Phe Leu Cys
130 135 140

Val Val Cys Ala Ile Val Pro Phe Arg Ser Lys Ile Leu Leu Ala Lys
145 150 155 160

35 Ala Glu Gly Glu Ile Ser Asp Pro Phe Arg Phe Thr Thr Phe Tyr Ile
165 170 175

His Phe Ala Leu Val Leu Ser Ala Leu Ile Leu Ala Cys Phe Arg Glu
180 185 190

40 Lys Pro Pro Phe Phe Ser Ala Lys Asn Val Asp Pro Asn Pro Tyr Pro
195 200 205

45 Glu Thr Ser Ala Gly Phe Leu Ser Arg Leu Phe Phe Trp Trp Phe Thr
210 215 220

Lys Met Ala Ile Tyr Gly Tyr Arg His Pro Leu Glu Lys Asp Leu
225 230 235 240

50 Trp Ser Leu Lys Glu Glu Asp Arg Ser Gln Met Val Val Gln Gln Leu
245 250 255

55 Leu Glu Ala Trp Arg Lys Gln Glu Lys Gln Thr Ala Arg His Lys Ala
260 265 270

EP 1 217 066 A1

Ser Ala Ala Pro Gly Lys Asn Ala Ser Gly Glu Asp Glu Val Leu Leu
 275 280 285
 5

Gly Ala Arg Pro Arg Pro Arg Lys Pro Ser Phe Leu Lys Ala Leu Leu
 290 295 300

10 Ala Thr Phe Gly Ser Ser Phe Leu Ile Ser Ala Cys Phe Lys Leu Ile
 305 310 315 320

Gln Asp Leu Leu Ser Phe Ile Asn Pro Gln Leu Leu Ser Ile Leu Ile
 15 325 330 335

Arg Phe Ile Ser Asn Pro Met Ala Pro Ser Trp Trp Gly Phe Leu Val
 340 345 350

20 Ala Gly Leu Met Phe Leu Cys Ser Met Met Gln Ser Leu Ile Leu Gln
 355 360 365

His Tyr Tyr His Tyr Ile Phe Val Thr Gly Val Lys Phe Arg Thr Gly
 25 370 375 380

Ile Met Gly Val Ile Tyr Arg Lys Ala Leu Val Ile Thr Asn Ser Val
 385 390 395 400

30 Lys Arg Ala Ser Thr Val Gly Glu Ile Val Asn Leu Met Ser Val Asp
 405 410 415

Ala Gln Arg Phe Met Asp Leu Ala Pro Phe Leu Asn Leu Leu Trp Ser
 35 420 425 430

Ala Pro Leu Gln Ile Ile Leu Ala Ile Tyr Phe Leu Trp Gln Asn Leu
 435 440 445

40 Gly Pro Ser Val Leu Ala Gly Val Ala Phe Met Val Leu Leu Ile Pro
 450 455 460

Leu Asn Gly Ala Val Ala Val Lys Met Arg Ala Phe Gln Val Lys Gln
 45 465 470 475 480

Met Lys Leu Lys Asp Ser Arg Ile Lys Leu Met Ser Glu Ile Leu Asn
 485 490 495

50 Gly Ile Lys Val Leu Lys Leu Tyr Ala Trp Glu Pro Ser Phe Leu Lys
 500 505 510

Gln Val Glu Gly Ile Arg Gln Gly Glu Leu Gln Leu Leu Arg Thr Ala
 55 515 520 525

EP 1 217 066 A1

Ala Tyr Leu His Thr Thr Thr Phe Thr Trp Met Cys Ser Pro Phe
530 535 540

5

Leu Val Thr Leu Ile Thr Leu Trp Val Tyr Val Tyr Val Asp Pro Asn
545 550 555 560

10 Asn Val Leu Asp Ala Glu Lys Ala Phe Val Ser Val Ser Leu Phe Asn
565 570 575

Ile Leu Arg Leu Pro Leu Asn Met Leu Pro Gln Leu Ile Ser Asn Leu
15 580 585 590

Thr Gln Ala Ser Val Ser Leu Lys Arg Ile Gln Gln Phe Leu Ser Gln
595 600 605

20 Glu Glu Leu Asp Pro Gln Ser Val Glu Arg Lys Thr Ile Ser Pro Gly
610 615 620

Tyr Ala Ile Thr Ile His Ser Gly Thr Phe Thr Trp Ala Gln Asp Leu
25 625 630 635 640

Pro Pro Thr Leu His Ser Leu Asp Ile Gln Val Pro Lys Gly Ala Leu
30 645 650 655

Val Ala Val Val Gly Pro Val Gly Cys Gly Lys Ser Ser Leu Val Ser
660 665 670

35 Ala Leu Leu Gly Glu Met Glu Lys Leu Glu Gly Lys Val His Met Lys
675 680 685

Gly Ser Val Ala Tyr Val Pro Gln Gln Ala Trp Ile Gln Asn Cys Thr
40 690 695 700

Leu Gln Glu Asn Val Leu Phe Gly Lys Ala Leu Asn Pro Lys Arg Tyr
705 710 715 720

45 Gln Gln Thr Leu Glu Ala Cys Ala Leu Leu Ala Asp Leu Glu Met Leu
725 730 735

Pro Gly Gly Asp Gln Thr Glu Ile Gly Glu Lys Gly Ile Asn Leu Ser
50 740 745 750

Gly Gly Gln Arg Gln Arg Val Ser Leu Ala Arg Ala Val Tyr Ser Asp
755 760 765

55 Ala Asp Ile Phe Leu Leu Asp Asp Pro Leu Ser Ala Val Asp Ser His
770 775 780

EP 1 217 066 A1

Val Ala Lys His Ile Phe Asp His Val Ile Gly Pro Glu Gly Val Leu
785 790 795 800
5
Ala Gly Lys Thr Arg Val Leu Val Thr His Gly Ile Ser Phe Leu Pro
805 810 815
10 Gln Thr Asp Phe Ile Ile Val Leu Ala Asp Gly Gln Val Ser Glu Met
820 825 830
Gly Pro Tyr Pro Ala Leu Leu Gln Arg Asn Gly Ser Phe Ala Asn Phe
835 840 845
15 Leu Cys Asn Tyr Ala Pro Asp Glu Asp Gln Gly His Leu Glu Asp Ser
850 855 860
20 Trp Thr Ala Leu Glu Gly Ala Glu Asp Lys Glu Ala Leu Leu Ile Glu
865 870 875 880
Asp Thr Leu Ser Asn His Thr Asp Leu Thr Asp Asn Asp Pro Val Thr
25 885 890 895
Tyr Val Val Gln Lys Gln Phe Met Arg Gln Leu Ser Ala Leu Ser Ser
900 905 910
30 Asp Gly Glu Gly Gln Gly Arg Pro Val Pro Arg Arg His Leu Gly Pro
915 920 925
Ser Glu Lys Val Gln Val Thr Glu Ala Lys Ala Asp Gly Ala Leu Thr
35 930 935 940
Gln Glu Glu Lys Ala Ala Ile Gly Thr Val Glu Leu Ser Val Phe Trp
945 950 955 960
40 Asp Tyr Ala Lys Ala Val Gly Leu Cys Thr Thr Leu Ala Ile Cys Leu
965 970 975
Leu Tyr Val Gly Gln Ser Ala Ala Ile Gly Ala Asn Val Trp Leu
45 980 985 990
Ser Ala Trp Thr Asn Asp Ala Met Ala Asp Ser Arg Gln Asn Asn Thr
995 1000 1005
50 Ser Leu Arg Leu Gly Val Tyr Ala Ala Leu Gly Ile Leu Gln Gly Phe
1010 1015 1020
Leu Val Met Leu Ala Ala Met Ala Met Ala Ala Gly Gly Ile Gln Ala
55 1025 1030 1035 1040

EP 1 217 066 A1

Ala Arg Val Leu His Gln Ala Leu Leu His Asn Lys Ile Arg Ser Pro
1045 1050 1055

5 Gln Ser Phe Phe Asp Thr Thr Pro Ser Gly Arg Ile Leu Asn Cys Phe
1060 1065 1070

10 Ser Lys Asp Ile Tyr Val Val Asp Glu Val Leu Ala Pro Val Ile Leu
1075 1080 1085

15 Met Leu Leu Asn Ser Phe Phe Asn Ala Ile Ser Thr Leu Val Val Ile
1090 1095 1100

Met Ala Ser Thr Pro Leu Phe Thr Val Val Ile Leu Pro Leu Ala Val
1105 1110 1115 1120

20 Leu Tyr Thr Leu Val Gln Arg Phe Tyr Ala Ala Thr Ser Arg Gln Leu
1125 1130 1135

25 Lys Arg Leu Glu Ser Val Ser Arg Ser Pro Ile Tyr Ser His Phe Ser
1140 1145 1150

Glu Thr Val Thr Gly Ala Ser Val Ile Arg Ala Tyr Asn Arg Ser Arg
1155 1160 1165

30 Asp Phe Glu Ile Ile Ser Asp Thr Lys Val Asp Ala Asn Gln Arg Ser
1170 1175 1180

35 Cys Tyr Pro Tyr Ile Ile Ser Asn Arg Trp Leu Ser Ile Gly Val Glu
1185 1190 1195 1200

Phe Val Gly Asn Cys Val Val Leu Phe Ala Ala Leu Phe Ala Val Ile
1205 1210 1215

40 Gly Arg Ser Ser Leu Asn Pro Gly Leu Val Gly Leu Ser Val Ser Tyr
1220 1225 1230

45 Ser Leu Gln Val Thr Phe Ala Leu Asn Trp Met Ile Arg Met Met Ser
1235 1240 1245

Asp Leu Glu Ser Asn Ile Val Ala Val Glu Arg Val Lys Glu Tyr Ser
1250 1255 1260

50 Lys Thr Glu Thr Glu Ala Pro Trp Val Val Glu Gly Ser Arg Pro Pro
1265 1270 1275 1280

55 Glu Gly Trp Pro Pro Arg Gly Glu Val Glu Phe Arg Asn Tyr Ser Val
1285 1290 1295

Arg Tyr Arg Pro Gly Leu Asp Leu Val Leu Arg Asp Leu Ser Leu His
 1300 1305 1310
 5

Val His Gly Gly Glu Lys Val Gly Ile Val Gly Arg Thr Gly Ala Gly
 1315 1320 1325

10 Lys Ser Ser Met Thr Leu Cys Leu Phe Arg Ile Leu Glu Ala Ala Lys
 1330 1335 1340

15 Gly Glu Ile Arg Ile Asp Gly Leu Asn Val Ala Asp Ile Gly Leu His
 1345 1350 1355 1360

Asp Leu Arg Ser Gln Leu Thr Ile Ile Pro Gln Asp Pro Ile Leu Phe
 1365 1370 1375

20 Ser Gly Thr Leu Arg Met Asn Leu Asp Pro Phe Gly Ser Tyr Ser Glu
 1380 1385 1390

25 Glu Asp Ile Trp Trp Ala Leu Glu Leu Ser His Leu His Thr Phe Val
 1395 1400 1405

30 Ser Ser Gln Pro Ala Gly Leu Asp Phe Gln Cys Ser Glu Gly Glu
 1410 1415 1420

Asn Leu Ser Val Gly Gln Arg Gln Leu Val Cys Leu Ala Arg Ala Leu
 1425 1430 1435 1440

35 Leu Arg Lys Ser Arg Ile Leu Val Leu Asp Glu Ala Thr Ala Ala Ile
 1445 1450 1455

Asp Leu Glu Thr Asp Asn Leu Ile Gln Ala Thr Ile Arg Thr Gln Phe
 1460 1465 1470

40 Asp Thr Cys Thr Val Leu Thr Ile Ala His Arg Leu Asn Thr Ile Met
 1475 1480 1485

45 Asp Tyr Thr Arg Val Leu Val Leu Asp Lys Gly Val Val Ala Glu Phe
 1490 1495 1500

Asp Ser Pro Ala Asn Leu Ile Ala Ala Arg Gly Ile Phe Tyr Gly Met
 50 1505 1510 1515 1520

Ala Arg Asp Ala Gly Leu Ala
 1525

EP 1 217 066 A1

<210> 63

<211> 1325

5 <212> PRT

<213> Homo sapiens

<400> 63

10 Met Leu Pro Val Tyr Gln Glu Val Lys Pro Asn Pro Leu Gln Asp Ala
1 5 10 15

15 Asn Ile Cys Ser Arg Val Phe Phe Trp Trp Leu Asn Pro Leu Phe Lys
20 25 30

Ile Gly His Lys Arg Arg Leu Glu Glu Asp Asp Met Tyr Ser Val Leu
35 40 45

20 Pro Glu Asp Arg Ser Gln His Leu Gly Glu Glu Leu Gln Gly Phe Trp
50 55 60

25 Asp Lys Glu Val Leu Arg Ala Glu Asn Asp Ala Gln Lys Pro Ser Leu
65 70 75 80

Thr Arg Ala Ile Ile Lys Cys Tyr Trp Lys Ser Tyr Leu Val Leu Gly
85 90 95

30 Ile Phe Thr Leu Ile Glu Glu Ser Ala Lys Val Ile Gln Pro Ile Phe
100 105 110

Leu Gly Lys Ile Ile Asn Tyr Phe Glu Asn Tyr Asp Pro Met Asp Ser
35 115 120 125

Val Ala Leu Asn Thr Ala Tyr Ala Tyr Ala Thr Val Leu Thr Phe Cys
130 135 140

40 Thr Leu Ile Leu Ala Ile Leu His His Leu Tyr Phe Tyr His Val Gln
145 150 155 160

45 Cys Ala Gly Met Arg Leu Arg Val Ala Met Cys His Met Ile Tyr Arg
165 170 175

Lys Ala Leu Arg Leu Ser Asn Met Ala Met Gly Lys Thr Thr Thr Gly
180 185 190

50 Gln Ile Val Asn Leu Leu Ser Asn Asp Val Asn Lys Phe Asp Gln Val
195 200 205

55 Thr Val Phe Leu His Phe Leu Trp Ala Gly Pro Leu Gln Ala Ile Ala
210 215 220

EP 1 217 066 A1

Val Thr Ala Leu Leu Trp Met Glu Ile Gly Ile Ser Cys Leu Ala Gly
225 230 235 240

5 Met Ala Val Leu Ile Ile Leu Leu Pro Leu Gln Ser Cys Phe Gly Lys
245 250 255

10 Leu Phe Ser Ser Leu Arg Ser' Lys Thr Ala Thr Phe Thr Asp Ala Arg
260 265 270

Ile Arg Thr Met Asn Glu Val Ile Thr Gly Ile Arg Ile Ile Lys Met
275 280 285

15 Tyr Ala Trp Glu Lys Ser Phe Ser Asn Leu Ile Thr Asn Leu Arg Lys
290 295 300

20 Lys Glu Ile Ser Lys Ile Leu Arg Ser Ser Cys Leu Arg Gly Met Asn
305 310 315 320

Leu Ala Ser Phe Phe Ser Ala Ser Lys Ile Ile Val Phe Val Thr Phe
25 325 330 335

Thr Thr Tyr Val Leu Leu Gly Ser Val Ile Thr Ala Ser Arg Val Phe
340 345 350

30 Val Ala Val Thr Leu Tyr Gly Ala Val Arg Leu Thr Val Thr Leu Phe
355 360 365

Phe Pro Ser Ala Ile Glu Arg Val Ser Glu Ala Ile Val Ser Ile Arg
35 370 375 380

Arg Ile Gln Thr Phe Leu Leu Leu Asp Glu Ile Ser Gln Arg Asn Arg
385 390 395 400

40 Gln Leu Pro Ser Asp Gly Lys Lys Met Val His Val Gln Asp Phe Thr
405 410 415

Ala Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr Leu Gln Gly Leu Ser
45 420 425 430

Phe Thr Val Arg Pro Gly Glu Leu Leu Ala Val Val Gly Pro Val Gly
435 440 445

50 Ala Gly Lys Ser Ser Leu Leu Ser Ala Val Leu Gly Glu Leu Ala Pro
450 455 460

Ser His Gly Leu Val Ser Val His Gly Arg Ile Ala Tyr Val Ser Gln
55 465 470 475 480

EP 1 217 066 A1

Gln Pro Trp Val Phe Ser Gly Thr Leu Arg Ser Asn Ile Leu Phe Gly
485 490 495

5 Lys Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val Ile Lys Ala Cys Ala
500 505 510

10 Leu Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly Asp Leu Thr Val Ile
515 520 525

15 Gly Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn
530 535 540

20 Leu Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile Tyr Leu Leu Asp Asp
545 550 555 560

25 Pro Leu Ser Ala Val Asp Ala Glu Val Ser Arg His Leu Phe Glu Leu
565 570 575

Cys Ile Cys Gln Ile Leu His Glu Lys Ile Thr Ile Leu Val Thr His
25 580 585 590

30 Gln Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile Leu Ile Leu Lys Asp
595 600 605

35 Gly Lys Met Val Gln Lys Gly Thr Tyr Thr Glu Phe Leu Lys Ser Gly
610 615 620

Ile Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn Glu Glu Ser Glu Gln
35 625 630 635 640

40 Pro Pro Val Pro Gly Thr Pro Thr Leu Arg Asn Arg Thr Phe Ser Glu
645 650 655

45 Ser Ser Val Trp Ser Gln Gln Ser Ser Arg Pro Ser Leu Lys Asp Gly
660 665 670

50 Ala Leu Glu Ser Gln Asp Thr Glu Asn Val Pro Val Thr Leu Ser Glu
675 680 685

Glu Asn Arg Ser Glu Gly Lys Val Gly Phe Gln Ala Tyr Lys Asn Tyr
690 695 700

55 Phe Arg Ala Gly Ala His Trp Ile Val Phe Ile Phe Leu Ile Leu Leu
705 710 715 720

Asn Thr Ala Ala Gln Val Ala Tyr Val Leu Gln Asp Trp Trp Leu Ser
725 730 735

EP 1 217 066 A1

Tyr Trp Ala Asn Lys Gln Ser Met Leu Asn Val Thr Val Asn Gly Gly
740 745 750

5 Gly Asn Val Thr Glu Lys Leu Asp Leu Asn Trp Tyr Leu Gly Ile Tyr
755 760 765

10 Ser Gly Leu Thr Val Ala Thr Val Leu Phe Gly Ile Ala Arg Ser Leu
770 775 780

15 Leu Val Phe Tyr Val Leu Val Asn Ser Ser Gln Thr Leu His Asn Lys
785 790 795 800

Met Phe Glu Ser Ile Leu Lys Ala Pro Val Leu Phe Phe Asp Arg Asn
805 810 815

20 Pro Ile Gly Arg Ile Leu Asn Arg Phe Ser Lys Asp Ile Gly His Leu
820 825 830

Asp Asp Leu Leu Pro Leu Thr Phe Leu Asp Phe Ile Gln Thr Leu Leu
25 835 840 845

Gln Val Val Gly Val Val Ser Val Ala Val Ala Val Ile Pro Trp Ile
850 855 860

30 Ala Ile Pro Leu Val Pro Leu Gly Ile Ile Phe Ile Phe Leu Arg Arg
865 870 875 880

Tyr Phe Leu Glu Thr Ser Arg Asp Val Lys Arg Leu Glu Ser Thr Thr
35 885 890 895

Arg Ser Pro Val Phe Ser His Leu Ser Ser Ser Leu Gln Gly Leu Trp
900 905 910

40 Thr Ile Arg Ala Tyr Lys Ala Glu Glu Arg Cys Gln Glu Leu Phe Asp
915 920 . 925

45 Ala His Gln Asp Leu His Ser Glu Ala Trp Phe Leu Phe Leu Thr Thr
930 935 940

Ser Arg Trp Phe Ala Val Arg Leu Asp Ala Ile Cys Ala Met Phe Val
945 950 955 960

50 Ile Ile Val Ala Phe Gly Ser Leu Ile Leu Ala Lys Thr Leu Asp Ala
965 970 975

55 Gly Gln Val Gly Leu Ala Leu Ser Tyr Ala Leu Thr Leu Met Gly Met
980 985 990

EP 1 217 066 A1

Phe Gln Trp Cys Val Arg Gln Ser Ala Glu Val Glu Asn Met Met Ile
995 1000 1005

5 Ser Val Glu Arg Val Ile Glu Tyr Thr Asp Leu Glu Lys Glu Ala Pro
1010 1015 1020

10 Trp Glu Tyr Gln Lys Arg Pro Pro Pro Ala Trp Pro His Glu Gly Val
1025 1030 1035 1040

Ile Ile Phe Asp Asn Val Asn Phe Met Tyr Ser Pro Gly Gly Pro Leu
1045 1050 1055

15 Val Leu Lys His Leu Thr Ala Leu Ile Lys Ser Gln Glu Lys Val Gly
1060 1065 1070

20 Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser Leu Ile Ser Ala Leu
1075 1080 1085

25 Phe Arg Leu Ser Glu Pro Glu Gly Lys Ile Trp Ile Asp Lys Ile Leu
1090 1095 1100

Thr Thr Glu Ile Gly Leu His Asp Leu Arg Lys Lys Met Ser Ile Ile
1105 1110 1115 1120

30 Pro Gln Glu Pro Val Leu Phe Thr Gly Thr Met Arg Lys Asn Leu Asp
1125 1130 1135

35 Pro Phe Lys Glu His Thr Asp Glu Glu Leu Trp Asn Ala Leu Gln Glu
1140 1145 1150

Val Gln Leu Lys Glu Thr Ile Glu Asp Leu Pro Gly Lys Met Asp Thr
1155 1160 1165

40 Glu Leu Ala Glu Ser Gly Ser Asn Phe Ser Val Gly Gln Arg Gln Leu
1170 1175 1180

45 Val Cys Leu Ala Arg Ala Ile Leu Arg Lys Asn Gln Ile Leu Ile Ile
1185 1190 1195 1200

Asp Glu Ala Thr Ala Asn Val Asp Pro Arg Thr Asp Glu Leu Ile Gln
1205 1210 1215

50 Lys Lys Ile Arg Glu Lys Phe Ala His Cys Thr Val Leu Thr Ile Ala
1220 1225 1230

His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys Ile Met Val Leu Asp
55 1235 1240 1245

EP 1217 066 A1

Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr Val Leu Leu Gln Asn
1250 1255 1260

5 Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln Leu Gly Lys Ala Glu
1265 1270 1275 1280

10 Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln Val Tyr Phe Lys Arg Asn
1285 1290 1295

Tyr Pro His Ile Gly His Thr Asp His Met Val Thr Asn Thr Ser Asn
1300 1305 1310

15 Gly Gln Pro Ser Thr Leu Thr Ile Phe Glu Thr Ala Leu
1315 1320 1325

20 <210> 64
<211> 1437
<212> PRT
25 <213> Homo sapiens

<400> 64
Met Lys Asp Ile Asp Ile Gly Lys Glu Tyr Ile Ile Pro Ser Pro Gly
30 1 5 10 15

Tyr Arg Ser Val Arg Glu Arg Thr Ser Thr Ser Gly Thr His Arg Asp
20 25 30

35 Arg Glu Asp Ser Lys Phe Arg Arg Thr Arg Pro Leu Glu Cys Gln Asp
35 40 45

40 Ala Leu Glu Thr Ala Ala Arg Ala Glu Gly Leu Ser Leu Asp Ala Ser
50 55 60

45 Met His Ser Gln Leu Arg Ile Leu Asp Glu Glu His Pro Lys Gly Lys
65 70 75 80

Tyr His His Gly Leu Ser Ala Leu Lys Pro Ile Arg Thr Thr Ser Lys
85 90 95

50 His Gln His Pro Val Asp Asn Ala Gly Leu Phe Ser Cys Met Thr Phe
100 105 110

55 Ser Trp Leu Ser Ser Leu Ala Arg Val Ala His Lys Lys Gly Glu Leu
115 120 125

Ser Met Glu Asp Val Trp Ser Leu Ser Lys His Glu Ser Ser Asp Val

EP 1 217 066 A1

	130	135	140
5	Asn Cys Arg Arg Leu Glu Arg Leu Trp Gln Glu Glu Leu Asn Glu Val		
	145	150	155
	Gly Pro Asp Ala Ala Ser Leu Arg Arg Val Val Trp Ile Phe Cys Arg		
10	165	170	175
	Thr Arg Leu Ile Leu Ser Ile Val Cys Leu Met Ile Thr Gln Leu Ala		
	180	185	190
15	Gly Phe Ser Gly Pro Ala Phe Met Val Lys His Leu Leu Glu Tyr Thr		
	195	200	205
	Gln Ala Thr Glu Ser Asn Leu Gln Tyr Ser Leu Leu Leu Val Leu Gly		
20	210	215	220
	Leu Leu Leu Thr Glu Ile Val Arg Ser Trp Ser Leu Ala Leu Thr Trp		
	225	230	235
25	Ala Leu Asn Tyr Arg Thr Gly Val Arg Leu Arg Gly Ala Ile Leu Thr		
	245	250	255
	Met Ala Phe Lys Lys Ile Leu Lys Leu Lys Asn Ile Lys Glu Lys Ser		
30	260	265	270
	Leu Gly Glu Leu Ile Asn Ile Cys Ser Asn Asp Gly Gln Arg Met Phe		
	275	280	285
35	Glu Ala Ala Ala Val Gly Ser Leu Leu Ala Gly Gly Pro Val Val Ala		
	290	295	300
	Ile Leu Gly Met Ile Tyr Asn Val Ile Ile Leu Gly Pro Thr Gly Phe		
40	305	310	315
	Leu Gly Ser Ala Val Phe Ile Leu Phe Tyr Pro Ala Met Met Phe Ala		
	325	330	335
45	Ser Arg Leu Thr Ala Tyr Phe Arg Arg Lys Cys Val Ala Ala Thr Asp		
	340	345	350
	Glu Arg Val Gln Lys Met Asn Glu Val Leu Thr Tyr Ile Lys Phe Ile		
50	355	360	365
	Lys Met Tyr Ala Trp Val Lys Ala Phe Ser Gln Ser Val Gln Lys Ile		
	370	375	380
55	Arg Glu Glu Glu Arg Arg Ile Leu Glu Lys Ala Gly Tyr Phe Gln Gly		

EP 1 217 066 A1

	385	390	395	400
5	Ile Thr Val Gly Val Ala Pro Ile Val Val Val Ile Ala Ser Val Val			
	405	410		415
	Thr Phe Ser Val His Met Thr Leu Gly Phe Asp Leu Thr Ala Ala Gln			
10	420	425		430
	Ala Phe Thr Val Val Thr Val Phe Asn Ser Met Thr Phe Ala Leu Lys			
	435	440		445
15	Val Thr Pro Phe Ser Val Lys Ser Leu Ser Glu Ala Ser Val Ala Val			
	450	455	460	
	Asp Arg Phe Lys Ser Leu Phe Leu Met Glu Glu Val His Met Ile Lys			
20	465	470	475	480
	Asn Lys Pro Ala Ser Pro His Ile Lys Ile Glu Met Lys Asn Ala Thr			
	485	490		495
25	Ieu Ala Trp Asp Ser Ser His Ser Ser Ile Gln Asn Ser Pro Lys Leu			
	500	505		510
	Thr Pro Lys Met Lys Lys Asp Lys Arg Ala Ser Arg Gly Lys Lys Glu			
30	515	520		525
	Lys Val Arg Gln Leu Gln Arg Thr Glu His Gln Ala Val Leu Ala Glu			
	530	535	540	
35	Gln Lys Gly His Leu Leu Leu Asp Ser Asp Glu Arg Pro Ser Pro Glu			
	545	550	555	560
	Glu Glu Glu Gly Lys His Ile His Leu Gly His Leu Arg Leu Gln Arg			
40	565	570		575
	Thr Leu His Ser Ile Asp Leu Glu Ile Gln Glu Gly Lys Leu Val Gly			
	580	585		590
45	Ile Cys Gly Ser Val Gly Ser Gly Lys Thr Ser Leu Ile Ser Ala Ile			
	595	600	605	
	Leu Gly Gln Met Thr Leu Leu Glu Gly Ser Ile Ala Ile Ser Gly Thr			
50	610	615	620	
	Phe Ala Tyr Val Ala Gln Gln Ala Trp Ile Leu Asn Ala Thr Leu Arg			
	625	630	635	640
55	Asp Asn Ile Leu Phe Gly Lys Glu Tyr Asp Glu Glu Arg Tyr Asn Ser			

EP 1 217 066 A1

	645	650	655
5	Val Leu Asn Ser Cys Cys Leu Arg Pro Asp Leu Ala Ile Leu Pro Ser 660	665	670
	Ser Asp Leu Thr Glu Ile Gly Glu Arg Gly Ala Asn Leu Ser Gly Gly 675	680	685
10	Gln Arg Gln Arg Ile Ser Leu Ala Arg Ala Leu Tyr Ser Asp Arg Ser 690	695	700
	Ile Tyr Ile Leu Asp Asp Pro Leu Ser Ala Leu Asp Ala His Val Gly 705	710	715
15	Asn His Ile Phe Asn Ser Ala Ile Arg Lys His Leu Lys Ser Lys Thr 725	730	735
20	Val Leu Phe Val Thr His Gln Leu Gln Tyr Leu Val Asp Cys Asp Glu 740	745	750
	Val Ile Phe Met Lys Glu Gly Cys Ile Thr Glu Arg Gly Thr His Glu 755	760	765
25	Glu Leu Met Asn Leu Asn Gly Asp Tyr Ala Thr Ile Phe Asn Asn Leu 770	775	780
30	Leu Leu Gly Glu Thr Pro Pro Val Glu Ile Asn Ser Lys Lys Glu Thr 785	790	795
	Ser Gly Ser Gln Lys Lys Ser Gln Asp Lys Gly Pro Lys Thr Gly Ser 805	810	815
35	Val Lys Lys Glu Lys Ala Val Lys Pro Glu Glu Gly Gln Leu Val Gln 820	825	830
40	Leu Glu Glu Lys Gly Gln Gly Ser Val Pro Trp Ser Val Tyr Gly Val 835	840	845
	Tyr Ile Gln Ala Ala Gly Gly Pro Leu Ala Phe Leu Val Ile Met Ala 850	855	860
45	Leu Phe Met Leu Asn Val Gly Ser Thr Ala Phe Ser Thr Trp Trp Leu 865	870	875
50	Ser Tyr Trp Ile Lys Gln Gly Ser Gly Asn Thr Thr Val Thr Arg Gly 885	890	895
55	Asn Glu Thr Ser Val Ser Asp Ser Met Lys Asp Asn Pro His Met Gln		

EP 1 217 066 A1

	900	905	910
5	Tyr Tyr Ala Ser Ile Tyr Ala Leu Ser Met Ala Val Met Leu Ile Leu 915	920	925
10	Lys Ala Ile Arg Gly Val Val Phe Val Lys Gly Thr Leu Arg Ala Ser 930	935	940
	Ser Arg Leu His Asp Glu Leu Phe Arg Arg Ile Leu Arg Ser Pro Met 945	950	955
15	Lys Phe Phe Asp Thr Thr Pro Thr Gly Arg Ile Leu Asn Arg Phe Ser 965	970	975
20	Lys Asp Met Asp Glu Val Asp Val Arg Leu Pro Phe Gln Ala Glu Met 980	985	990
	Phe Ile Gln Asn Val Ile Leu Val Phe Phe Cys Val Gly Met Ile Ala 995	1000	1005
25	Gly Val Phe Pro Trp Phe Leu Val Ala Val Gly Pro Leu Val Ile Leu 1010	1015	1020
30	Phe Ser Val Leu His Ile Val Ser Arg Val Leu Ile Arg Glu Leu Lys 1025	1030	1035
	Arg Leu Asp Asn Ile Thr Gln Ser Pro Phe Leu Ser His Ile Thr Ser 1045	1050	1055
35	Ser Ile Gln Gly Leu Ala Thr Ile His Ala Tyr Asn Lys Gly Gln Glu 1060	1065	1070
40	Phe Leu His Arg Tyr Gln Glu Leu Leu Asp Asp Asn Gln Ala Pro Phe 1075	1080	1085
	Phe Leu Phe Thr Cys Ala Met Arg Trp Leu Ala Val Arg Leu Asp Leu 1090	1095	1100
45	Ile Ser Ile Ala Leu Ile Thr Thr Thr Gly Leu Met Ile Val Leu Met 1105	1110	1115
50	His Gly Gln Ile Pro Pro Ala Tyr Ala Gly Leu Ala Ile Ser Tyr Ala 1125	1130	1135
	Val Gln Leu Thr Gly Leu Phe Gln Phe Thr Val Arg Leu Ala Ser Glu 1140	1145	1150
55	Thr Glu Ala Arg Phe Thr Ser Val Glu Arg Ile Asn His Tyr Ile Lys		

EP 1 217 066 A1

	1155	1160	1165
5	Thr Leu Ser Leu Glu Ala Pro Ala Arg Ile Lys Asn Lys Ala Pro Ser		
	1170	1175	1180
	Pro Asp Trp Pro Gln Glu Gly Glu Val Thr Phe Glu Asn Ala Glu Met		
10	1185	1190	1195
	Arg Tyr Arg Glu Asn Leu Pro Leu Val Leu Lys Lys Val Ser Phe Thr		
	1205	1210	1215
15	Ile Lys Pro Lys Glu Lys Ile Gly Ile Val Gly Arg Thr Gly Ser Gly		
	1220	1225	1230
	Lys Ser Ser Leu Gly Met Ala Leu Phe Arg Leu Val Glu Leu Ser Gly		
20	1235	1240	1245
	Gly Cys Ile Lys Ile Asp Gly Val Arg Ile Ser Asp Ile Gly Leu Ala		
	1250	1255	1260
25	Asp Leu Arg Ser Lys Leu Ser Ile Ile Pro Gln Glu Pro Val Leu Phe		
	1265	1270	1275
	Ser Gly Thr Val Arg Ser Asn Leu Asp Pro Phe Asn Gln Tyr Thr Glu		
30	1285	1290	1295
	Asp Gln Ile Trp Asp Ala Leu Glu Arg Thr His Met Lys Glu Cys Ile		
	1300	1305	1310
35	Ala Gln Leu Pro Leu Lys Leu Glu Ser Glu Val Met Glu Asn Gly Asp		
	1315	1320	1325
	Asn Phe Ser Val Gly Glu Arg Gln Leu Leu Cys Ile Ala Arg Ala Leu		
40	1330	1335	1340
	Leu Arg His Cys Lys Ile Leu Ile Leu Asp Glu Ala Thr Ala Ala Met		
	1345	1350	1355
	Asp Thr Glu Thr Asp Leu Leu Ile Gln Glu Thr Ile Arg Glu Ala Phe		
45	1365	1370	1375
	Ala Asp Cys Thr Met Leu Thr Ile Ala His Arg Leu His Thr Val Leu		
50	1380	1385	1390
	Gly Ser Asp Arg Ile Met Val Leu Ala Gln Gly Gln Val Val Glu Phe		
	1395	1400	1405
55	Asp Thr Pro Ser Val Leu Leu Ser Asn Asp Ser Ser Arg Phe Tyr Ala		

EP 1 217 066 A1

	1410	1415	1420
5	Met Phe Ala Ala Ala Glu Asn Lys Val Ala Val Lys Gly		
	1425	1430	1435
10	<210> 65		
	<211> 1503		
	<212> PRT		
	<213> Homo sapiens		
15	<400> 65		
	Met Ala Ala Pro Ala Glu Pro Cys Ala Gly Gln Gly Val Trp Asn Gln		
	1	5	10
20	Thr Glu Pro Glu Pro Ala Ala Thr Ser Leu Leu Ser Leu Cys Phe Leu		
	20	25	30
25	Arg Thr Ala Gly Val Trp Val Pro Pro Met Tyr Leu Trp Val Leu Gly		
	35	40	45
	Pro Ile Tyr Leu Leu Phe Ile His His His Gly Arg Gly Tyr Leu Trp		
	50	55	60
30			
	Met Ser Pro Leu Phe Lys Ala Lys Met Val Leu Gly Phe Ala Leu Ile		
	65	70	75
35	Val Leu Cys Thr Ser Ser Val Ala Val Ala Leu Trp Lys Ile Gln Gln		
	85	90	95
	Gly Thr Pro Glu Ala Pro Glu Phe Leu Ile His Pro Thr Val Trp Leu		
	100	105	110
40			
	Thr Thr Met Ser Phe Ala Val Phe Leu Ile His Thr Glu Arg Lys Lys		
	115	120	125
45	Gly Val Gln Ser Ser Gly Val Leu Phe Gly Tyr Trp Leu Leu Cys Phe		
	130	135	140
	Val Leu Pro Ala Thr Asn Ala Ala Gln Gln Ala Ser Gly Ala Gly Phe		
	145	150	155
50	160		
	Gln Ser Asp Pro Val Arg His Leu Ser Thr Tyr Leu Cys Leu Ser Leu		
	165	170	175
55	Val Val Ala Gln Phe Val Leu Ser Cys Leu Ala Asp Gln Pro Pro Phe		
	180	185	190

EP 1 217 066 A1

Phe Pro Glu Asp Pro Gln Gln Ser Asn Pro Cys Pro Glu Thr Gly Ala
5 195 200 205

Ala Phe Pro Ser Lys Ala Thr Phe Trp Trp Val Ser Gly Leu Val Trp
10 210 215 220

Arg Gly Tyr Arg Arg Pro Leu Arg Pro Lys Asp Leu Trp Ser Leu Gly
15 225 230 235 240

Arg Glu Asn Ser Ser Glu Glu Leu Val Ser Arg Leu Glu Lys Glu Trp
20 245 250 255

Met Arg Asn Arg Ser Ala Ala Arg Arg His Asn Lys Ala Ile Ala Phe
25 260 265 270

Lys Arg Lys Gly Gly Ser Gly Met Lys Ala Pro Glu Thr Glu Pro Phe
20 275 280 285

Leu Arg Gln Glu Gly Ser Gln Trp Arg Pro Leu Leu Lys Ala Ile Trp
25 290 295 300

Gln Val Phe His Ser Thr Phe Leu Leu Gly Thr Leu Ser Leu Ile Ile
30 305 310 315 320

Ser Asp Val Phe Arg Phe Thr Val Pro Lys Leu Leu Ser Leu Phe Leu
35 325 330 335

Glu Phe Ile Gly Asp Pro Lys Pro Pro Ala Trp Lys Gly Tyr Leu Leu
35 340 345 350

Ala Val Leu Met Phe Leu Ser Ala Cys Leu Gln Thr Leu Phe Glu Gln
40 355 360 365

Gln Asn Met Tyr Arg Leu Lys Val Leu Gln Met Arg Leu Arg Ser Ala
45 370 375 380

Ile Thr Gly Leu Val Tyr Arg Lys Val Leu Ala Leu Ser Ser Gly Ser
40 385 390 395 400

Arg Lys Ala Ser Ala Val Gly Asp Val Val Asn Leu Val Ser Val Asp
45 405 410 415

Val Gln Arg Leu Thr Glu Ser Val Leu Tyr Leu Asn Gly Leu Trp Leu
50 420 425 430

Pro Leu Val Trp Ile Val Val Cys Phe Val Tyr Leu Trp Gln Leu Leu
55 435 440 445

EP 1 217 066 A1

Gly Pro Ser Ala Leu Thr Ala Ile Ala Val Phe Leu Ser Leu Leu Pro
5 450 455 460

Leu Asn Phe Phe Ile Ser Lys Lys Arg Asn His His Gln Glu Glu Gln
465 470 475 480

10 Met Arg Gln Lys Asp Ser Arg Ala Arg Leu Thr Ser Ser Ile Leu Arg
485 490 495

Asn Ser Lys Thr Ile Lys Phe His Gly Trp Glu Gly Ala Phe Leu Asp
15 500 505 510

Arg Val Leu Gly Ile Arg Gly Gln Glu Leu Gly Ala Leu Arg Thr Ser
515 520 525

20 Gly Leu Leu Phe Ser Val Ser Leu Val Ser Phe Gln Val Ser Thr Phe
530 535 540

Leu Val Ala Leu Val Val Phe Ala Val His Thr Leu Val Ala Glu Asn
25 545 550 555 560

Ala Met Asn Ala Glu Lys Ala Phe Val Thr Leu Thr Val Leu Asn Ile
565 570 575

30 Leu Asn Lys Ala Gln Ala Phe Leu Pro Phe Ser Ile His Ser Leu Val
580 585 590

Gln Ala Arg Val Ser Phe Asp Arg Leu Val Thr Phe Leu Cys Leu Glu
35 595 600 605

Glu Val Asp Pro Gly Val Val Asp Ser Ser Ser Ser Gly Ser Ala Ala
610 615 620

40 Gly Lys Asp Cys Ile Thr Ile His Ser Ala Thr Phe Ala Trp Ser Gln
625 630 635 640

Glu Ser Pro Pro Cys Leu His Arg Ile Asn Leu Thr Val Pro Gln Gly
45 645 650 655

Cys Leu Leu Ala Val Val Gly Pro Val Gly Ala Gly Lys Ser Ser Leu
50 660 665 670

Leu Ser Ala Leu Leu Gly Glu Leu Ser Lys Val Glu Gly Phe Val Ser
675 680 685

Ile Glu Gly Ala Val Ala Tyr Val Pro Gln Glu Ala Trp Val Gln Asn
55 690 695 700

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

RECEIVED

MAR 31 2006
4 of 5

To:
BARRY L. DAVISON
2600 CENTURY SQUARE
1501 FOURTH AVENUE
SEATTLE, WA 98101-1688

PCT

**NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION**

(PCT Rule 44.1)

		Date of mailing (day/month/year) 29 MAR 2006
Applicant's or agent's file reference 55382-28		FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US05/14668		International filing date (day/month/year) 27 April 2005 (27.04.2005)
Applicant ILLUMIGEN BIOSCIENCES, INC.		

1. The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments shall normally two months from the date of transmittal of the international

Where? Directly to the International Bureau, 1211 Geneva 20, Switzerland.

For example, if the application is filed in the United States, the amendment sheet must be submitted with the application.

2. The applicant is entitled to request that the declaration under Article 19(1) be established and that the declaration under Article 19(2) be transmitted to the International Searching Authority are transmitted herewith.

3. If the applicant fails to pay the additional fee(s) under Rule 40.2, the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

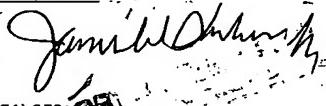
Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer David Humphrey Telephone No. (571) 272-6000  <i>Please note on accompanying sheet</i>
--	---

Form PCT/ISA/220 (January 2004)

EP 1 217 066 A1

EP 1 217 066 A1

5	Ser Phe Cys Arg Gly Tyr Trp Leu Ser Leu Trp Ala Asp Asp Pro Ala 965	970	975
	Val Gly Gly Gln Gln Thr Gln Ala Ala Leu Arg Gly Gly Ile Phe Gly 980	985	990
10	Leu Leu Gly Cys Leu Gln Ala Ile Gly Leu Phe Ala Ser Met Ala Ala 995	1000	1005
	Val Leu Leu Gly Gly Ala Arg Ala Ser Arg Leu Leu Phe Gln Arg Leu 1010	1015	1020
15	Leu Trp Asp Val Val Arg Ser Pro Ile Ser Phe Phe Glu Arg Thr Pro 1025	1030	1035
	Ile Gly His Leu Leu Asn Arg Phe Ser Lys Glu Thr Asp Thr Val Asp 1045	1050	1055
20	Val Asp Ile Pro Asp Lys Leu Arg Ser Leu Leu Met Tyr Ala Phe Gly 1060	1065	1070
	Leu Leu Glu Val Ser Leu Val Val Ala Val Ala Thr Pro Leu Ala Thr 1075	1080	1085
25	Val Ala Ile Leu Pro Leu Phe Leu Leu Tyr Ala Gly Phe Gln Ser Leu 1090	1095	1100
	Tyr Val Val Ser Ser Cys Gln Leu Arg Arg Leu Glu Ser Ala Ser Tyr 1105	1110	1115
30	Ser Ser Val Cys Ser His Met Ala Glu Thr Phe Gln Gly Ser Thr Val 1125	1130	1135
	Val Arg Ala Phe Arg Thr Gln Ala Pro Phe Val Ala Gln Asn Asn Ala 1140	1145	1150
35	Arg Val Asp Glu Ser Gln Arg Ile Ser Phe Pro Arg Leu Val Ala Asp 1155	1160	1165
	Arg Trp Leu Ala Ala Asn Val Glu Leu Leu Gly Asn Gly Leu Val Phe 1170	1175	1180
40	Ala Ala Ala Thr Cys Ala Val Leu Ser Lys Ala His Leu Ser Ala Gly 1185	1190	1195
	Leu Val Gly Phe Ser Val Ser Ala Ala Leu Gln Val Thr Gln Thr Leu 1205	1210	1215

EP 1217 066 A1

Gln Trp Val Val Arg Asn Trp Thr Asp Leu Glu Asn Ser Ile Val Ser
 1220 1225 1230
 5

Val Glu Arg Met Gln Asp Tyr Ala Trp Thr Pro Lys Glu Ala Pro Trp
 1235 1240 1245

10 Arg Leu Pro Thr Cys Ala Ala Gln Pro Pro Trp Pro Gln Gly Gly Gln
 1250 1255 1260

15 Ile Glu Phe Arg Asp Phe Gly Leu Arg Tyr Arg Pro Glu Leu Pro Leu
 1265 1270 1275 1280

Ala Val Gln Gly Val Ser Phe Lys Ile His Ala Gly Glu Lys Val Gly
 1285 1290 1295

20 Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser Leu Ala Ser Gly Leu
 1300 1305 1310

25 Leu Arg Leu Gln Glu Ala Ala Glu Gly Gly Ile Trp Ile Asp Gly Val
 1315 1320 1325

Pro Ile Ala His Val Gly Leu His Thr Leu Arg Ser Arg Ile Ser Ile
 1330 1335 1340

30 Ile Pro Gln Asp Pro Ile Leu Phe Pro Gly Ser Leu Arg Met Asn Leu
 1345 1350 1355 1360

35 Asp Leu Leu Gln Glu His Ser Asp Glu Ala Ile Trp Ala Ala Leu Glu
 1365 1370 1375

Thr Val Gln Leu Lys Ala Leu Val Ala Ser Leu Pro Gly Gln Leu Gln
 1380 1385 1390

40 Tyr Lys Cys Ala Asp Arg Gly Glu Asp Leu Ser Val Gly Gln Lys Gln
 1395 1400 1405

45 Leu Leu Cys Leu Ala Arg Ala Leu Leu Arg Lys Thr Gln Ile Leu Ile
 1410 1415 1420

50 Leu Asp Glu Ala Thr Ala Ala Val Asp Pro Gly Thr Glu Leu Gln Met
 1425 1430 1435 1440

Gln Ala Met Leu Gly Ser Trp Phe Ala Gln Cys Thr Val Leu Leu Ile
 1445 1450 1455

55 Ala His Arg Leu Arg Ser Val Met Asp Cys Ala Arg Val Leu Val Met
 1460 1465 1470

EP 1 217 066 A1

Asp Lys Gly Gln Val Ala Glu Ser Gly Ser Pro Ala Gln Leu Leu Ala
1475 1480 1485

5

Gln Lys Gly Leu Phe Tyr Arg Leu Ala Gln Glu Ser Gly Leu Val
1490 1495 1500

10

<210> 66

<211> 1480

<212> PRT

15

<213> Homo sapiens

<400> 66

Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser Lys Leu Phe
20 5 10 15

Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg Gln Arg Leu
25 20 25 30

25

Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser Ala Asp Asn
35 40 45

30

Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu Ala Ser Lys
50 55 60

35

Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe Phe Trp Arg
65 70 75 80

35

Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val Thr Lys Ala
85 90 95

40

Val Gln Pro Leu Leu Gly Arg Ile Ile Ala Ser Tyr Asp Pro Asp
100 105 110

45

Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile Gly Leu Cys
115 120 125

50

Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala Ile Phe Gly
130 135 140

55

Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe Ser Leu Ile
145 150 155 160

55

Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp Lys Ile Ser
165 170 175

EP 1 217 066 A1

Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn Lys Phe Asp
180 185 190

5 Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro Leu Gln Val
195 200 205

10 Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala Ser Ala Phe
210 215 220

15 Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln Ala Gly Leu
225 230 235 240

Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly Lys Ile Ser
245 250 255

20 Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile Gln Ser Val
260 265 270

Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile Glu Asn Leu
275 280 285

25 Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr Val Arg Tyr
290 295 300

30 Phe Asn Ser Ser Ala Phe Phe Ser Gly Phe Phe Val Val Phe Leu
305 310 315 320

Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu Arg Lys Ile
325 330 335

35 Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala Val Thr Arg
340 345 350

40 Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu Gly Ala Ile
355 360 365

45 Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys Thr Leu Glu
370 375 380

Tyr Asn Leu Thr Thr Glu Val Val Met Glu Asn Val Thr Ala Phe
385 390 395 400

50 Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys Gln Asn Asn
405 410 415

55 Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe Phe Ser Asn
420 425 430

EP 1 217 066 A1

Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn Phe Lys Ile
435 440 445

5 Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly Ala Gly Lys
450 455 460

10 Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro Ser Glu Gly
465 470 475 480

15 Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln Phe Ser Trp
485 490 495

Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly Val Ser Tyr
500 505 510

20 Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln Leu Glu Glu
515 520 525

Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu Gly Glu Gly
25 530 535 540

Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser Leu Ala Arg
545 550 555 560

30 Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser Pro Phe Gly
565 570 575

Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser Cys Val Cys
35 580 585 590

Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser Lys Met Glu
595 600 605

40 His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu Gly Ser Ser
610 615 620

Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln Pro Asp Phe
45 625 630 635 640

Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe Ser Ala Glu
645 650 655

50 Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe Ser Leu Glu
660 665 670

Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln Ser Phe Lys
55 675 680 685

EP 1 217 066 A1

Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile Leu Asn Pro
690 695 700

5 Ile Asn Ser Ile Arg Lys Phe Ser Ile Val Gln Lys Thr Pro Leu Gln
705 710 715 720

10 Met Asn Gly Ile Glu Glu Asp Ser Asp Glu Pro Leu Glu Arg Arg Leu
725 730 735

Ser Leu Val Pro Asp Ser Glu Gln Gly Glu Ala Ile Leu Pro Arg Ile
740 745 750

15 Ser Val Ile Ser Thr Gly Pro Thr Leu Gln Ala Arg Arg Arg Gln Ser
755 760 765

20 Val Leu Asn Leu Met Thr His Ser Val Asn Gln Gly Gln Asn Ile His
770 775 780

Arg Lys Thr Thr Ala Ser Thr Arg Lys Val Ser Leu Ala Pro Gln Ala
25 785 790 795 800

Asn Leu Thr Glu Leu Asp Ile Tyr Ser Arg Arg Leu Ser Gln Glu Thr
805 810 815

30 Gly Leu Glu Ile Ser Glu Glu Ile Asn Glu Glu Asp Leu Lys Glu Cys
820 825 830

Phe Phe Asp Asp Met Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr
35 835 840 845

Tyr Leu Arg Tyr Ile Thr Val His Lys Ser Leu Ile Phe Val Leu Ile
850 855 860

40 Trp Cys Leu Val Ile Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val
865 870 875 880

Leu Trp Leu Leu Gly Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr
45 885 890 895

His Ser Arg Asn Asn Ser Tyr Ala Val Ile Ile Thr Ser Thr Ser Ser
900 905 910

50 Tyr Tyr Val Phe Tyr Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala
915 920 925

55 Met Gly Phe Phe Arg Gly Leu Pro Leu Val His Thr Leu Ile Thr Val
930 935 940

EP 1 217 066 A1

Ser Lys Ile Leu His His Lys Met Leu His Ser Val Leu Gln Ala Pro
 945 950 955 960
 5 Met Ser Thr Leu Asn Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe
 965 970 975
 10 Ser Lys Asp Ile Ala Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe
 980 985 990
 Asp Phe Ile Gln Leu Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val
 995 1000 1005
 15 Ala Val Leu Gln Pro Tyr Ile Phe Val Ala Thr Val Pro Val Ile Val
 1010 1015 1020
 20 Ala Phe Ile Met Leu Arg Ala Tyr Phe Leu Gln Thr Ser Gln Gln Leu
 1025 1030 1035 1040
 Lys Gln Leu Glu Ser Glu Gly Arg Ser Pro Ile Phe Thr His Leu Val
 25 1045 1050 1055
 Thr Ser Leu Lys Gly Leu Trp Thr Leu Arg Ala Phe Gly Arg Gln Pro
 1060 1065 1070
 30 Tyr Phe Glu Thr Leu Phe His Lys Ala Leu Asn Leu His Thr Ala Asn
 1075 1080 1085
 Trp Phe Leu Tyr Leu Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu
 35 1090 1095 1100
 Met Ile Phe Val Ile Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu
 1105 1110 1115 1120
 40 Thr Thr Gly Glu Gly Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala
 1125 1130 1135
 Met Asn Ile Met Ser Thr Leu Gln Trp Ala Val Asn Ser Ser Ile Asp
 45 1140 1145 1150
 Val Asp Ser Leu Met Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp
 1155 1160 1165
 50 Met Pro Thr Glu Gly Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn
 1170 1175 1180
 Gly Gln Leu Ser Lys Val Met Ile Ile Glu Asn Ser His Val Lys Lys
 55 1185 1190 1195 1200

Asp Asp Ile Trp Pro Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr
 1205 1210 1215
 5 Ala Lys Tyr Thr Glu Gly Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe
 1220 1225 1230
 10 Ser Ile Ser Pro Gly Gln Arg Val Gly Leu Leu Gly Arg Thr Gly Ser
 1235 1240 1245
 15 Gly Lys Ser Thr Leu Leu Ser Ala Phe Leu Arg Leu Leu Asn Thr Glu
 1250 1255 1260
 20 Gly Glu Ile Gln Ile Asp Gly Val Ser Trp Asp Ser Ile Thr Leu Gln
 1265 1270 1275 1280
 25 Gln Trp Arg Lys Ala Phe Gly Val Ile Pro Gln Lys Val Phe Ile Phe
 1285 1290 1295
 30 Ser Gly Thr Phe Arg Lys Asn Leu Asp Pro Tyr Glu Gln Trp Ser Asp
 1300 1305 1310
 35 Gln Glu Ile Trp Lys Val Ala Asp Glu Val Gly Leu Arg Ser Val Ile
 1315 1320 1325
 40 Glu Gln Phe Pro Gly Lys Leu Asp Phe Val Leu Val Asp Gly Gly Cys
 1330 1335 1340
 45 Val Leu Ser His Gly His Lys Gln Leu Met Cys Leu Ala Arg Ser Val
 1345 1350 1355 1360
 50 Leu Ser Lys Ala Lys Ile Leu Leu Leu Asp Glu Pro Ser Ala His Leu
 1365 1370 1375
 55 Asp Pro Val Thr Tyr Gln Ile Ile Arg Arg Thr Leu Lys Gln Ala Phe
 1380 1385 1390
 Ala Asp Cys Thr Val Ile Leu Cys Glu His Arg Ile Glu Ala Met Leu
 1395 1400 1405
 60 Glu Cys Gln Gln Phe Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr
 1410 1415 1420
 65 Asp Ser Ile Gln Lys Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala
 1425 1430 1435 1440
 70 Ile Ser Pro Ser Asp Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser
 1445 1450 1455

EP 1 217 066 A1

Lys Cys Lys Ser Lys Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu
1460 1465 1470

5 Glu Glu Val Gln Asp Thr Arg Leu
 1475 1480

10 <210> 67
 <211> 1581
 <212> PRT
15 <213> Homo sapiens

20 <400> 67
Met Pro Leu Ala Phe Cys Gly Ser Glu Asn His Ser Ala Ala Tyr Arg
1 5 10 15

Val Asp Gln Gly Val Leu Asn Asn Gly Cys Phe Val Asp Ala Leu Asn
20 25 30

25 Val Val Pro His Val Phe Leu Leu Phe Ile Thr Phe Pro Ile Leu Phe
 35 40 45

30 Ile Gly Trp Gly Ser Gln Ser Ser Lys Val His Ile His His Ser Thr
 50 55 60

Trp Leu His Phe Pro Gly His Asn Leu Arg Trp Ile Leu Thr Phe Met
65 70 75 80

35 Leu Leu Phe Val Leu Val Cys Glu Ile Ala Glu Gly Ile Leu Ser Asp
 85 90 95

40 Gly Val Thr Glu Ser His His Leu His Leu Tyr Met Pro Ala Gly Met
 100 105 110

Ala Phe Met Ala Ala Val Thr Ser Val Val Tyr Tyr His Asn Ile Glu
115 120 125

45 Thr Ser Asn Phe Pro Lys Leu Leu Ile Ala Leu Leu Val Tyr Trp Thr
 130 135 140

50 Leu Ala Phe Ile Thr Lys Thr Ile Lys Phe Val Lys Leu Leu Asp His
 145 150 155 160

Ala Ile Gly Phe Ser Gln Leu Arg Phe Cys Leu Thr Gly Leu Leu Val
165 170 175

55 Ile Leu Tyr Gly Met Leu Leu Val Glu Val Asn Val Ile Arg Val

EP 1 217 066 A1

	180	185	190
5	Arg Arg Tyr Ile Phe Phe Lys Thr Pro Arg Glu Val Lys Pro Pro Glu		
	195	200	205
	Asp Leu Gln Asp Leu Gly Val Arg Phe Leu Gln Pro Phe Val Asn Leu		
10	210	215	220
	Pro Ser Lys Gly Thr Tyr Trp Trp Met Asn Ala Phe Ile Lys Thr Ala		
	225	230	235
	His Lys Lys Pro Ile Asp Leu Arg Ala Ile Gly Lys Leu Pro Ile Val		
15	245	250	255
	Met Arg Ala Leu Thr Asn Tyr Gln Arg Leu Cys Glu Ala Phe Asp Ala		
20	260	265	270
	Gln Val Arg Lys Asp Ile Gln Gly Thr Gln Gly Ala Arg Ala Ile Trp		
	275	280	285
25	Gln Ala Leu Ser His Ala Phe Gly Arg Arg Leu Val Leu Ser Ser Thr		
	290	295	300
	Phe Arg Ile Leu Ala Asp Leu Leu Gly Phe Ala Gly Pro Leu Cys Ile		
30	305	310	315
	Phe Gly Ile Val Asp His Leu Gly Lys Glu Asn Asp Val Phe Gln Pro		
	325	330	335
35	Lys Thr Gln Phe Leu Gly Val Tyr Phe Val Ser Ser Gln Glu Phe Leu		
	340	345	350
	Ala Asn Ala Tyr Val Leu Ala Val Leu Leu Phe Leu Ala Leu Leu Leu		
40	355	360	365
	Gln Arg Thr Phe Leu Gln Ala Ser Tyr Tyr Val Ala Ile Glu Thr Gly		
	370	375	380
45	Ile Asn Leu Arg Gly Ala Ile Gln Thr Lys Ile Tyr Asn Lys Ile Met		
	385	390	395
	His Leu Ser Thr Ser Asn Leu Ser Met Gly Glu Met Thr Ala Gly Gln		
50	405	410	415
	Ile Cys Asn Leu Val Ala Ile Asp Thr Asn Gln Leu Met Trp Phe Phe		
	420	425	430
55	Phe Leu Cys Pro Asn Leu Trp Ala Met Pro Val Gln Ile Ile Val Gly		

EP 1 217 066 A1

	435	440	445
5	Val Ile Leu Leu Tyr Tyr Ile Leu Gly Val Ser Ala Leu Ile Gly Ala		
	450	455	460
	Ala Val Ile Ile Leu Leu Ala Pro Val Gln Tyr Phe Val Ala Thr Lys		
10	465	470	475
	Leu Ser Gln Ala Gln Arg Ser Thr Leu Glu Tyr Ser Asn Glu Arg Leu		
	485	490	495
15	Lys Gln Thr Asn Glu Met Leu Arg Gly Ile Lys Leu Leu Lys Leu Tyr		
	500	505	510
	Ala Trp Glu Asn Ile Phe Arg Thr Arg Val Glu Thr Thr Arg Arg Lys		
20	515	520	525
	Glu Met Thr Ser Leu Arg Ala Phe Ala Ile Tyr Thr Ser Ile Ser Ile		
	530	535	540
25	Phe Met Asn Thr Ala Ile Pro Ile Ala Ala Val Leu Ile Thr Phe Val		
	545	550	555
	560		
	Gly His Val Ser Phe Phe Lys Glu Ala Asp Phe Ser Pro Ser Val Ala		
30	565	570	575
	Phe Ala Ser Leu Ser Leu Phe His Ile Leu Val Thr Pro Leu Phe Leu		
	580	585	590
35	Leu Ser Ser Val Val Arg Ser Thr Val Lys Ala Leu Val Ser Val Gln		
	595	600	605
	Lys Leu Ser Glu Phe Leu Ser Ser Ala Glu Ile Arg Glu Glu Gln Cys		
40	610	615	620
	Ala Pro His Glu Pro Thr Pro Gln Gly Pro Ala Ser Lys Tyr Gln Ala		
	625	630	635
	640		
45	Val Pro Leu Arg Val Val Asn Arg Lys Arg Pro Ala Arg Glu Asp Cys		
	645	650	655
	Arg Gly Leu Thr Gly Pro Leu Gln Ser Leu Val Pro Ser Ala Asp Gly		
50	660	665	670
	Asp Ala Asp Asn Cys Cys Val Gln Ile Met Gly Gly Tyr Phe Thr Trp		
	675	680	685
55	Thr Pro Asp Gly Ile Pro Thr Leu Ser Asn Ile Thr Ile Arg Ile Pro		

EP 1 217 066 A1

	690	695	700
5	Arg Gly Gln Leu Thr Met Ile Val Gly Gln Val Gly Cys Gly Lys Ser		
	705	710	715
	Ser Leu Leu Leu Ala Ala Leu Gly Glu Met Gln Lys Val Ser Gly Ala		
10	725	730	735
	Val Phe Trp Ser Ser Leu Pro Asp Ser Glu Ile Gly Glu Asp Pro Ser		
	740	745	750
15	Pro Glu Arg Glu Thr Ala Thr Asp Leu Asp Ile Arg Lys Arg Gly Pro		
	755	760	765
	Val Ala Tyr Ala Ser Gln Lys Pro Trp Leu Leu Asn Ala Thr Val Glu		
20	770	775	780
	Glu Asn Ile Ile Phe Glu Ser Pro Phe Asn Lys Gln Arg Tyr Lys Met		
	785	790	795
25	Val Ile Glu Ala Cys Ser Leu Gln Pro Asp Ile Asp Ile Leu Pro His		
	805	810	815
	Gly Asp Gln Thr Gln Ile Gly Glu Arg Gly Ile Asn Leu Ser Gly Gly		
30	820	825	830
	Gln Arg Gln Arg Ile Ser Val Ala Arg Ala Leu Tyr Gln His Ala Asn		
	835	840	845
35	Val Val Phe Leu Asp Asp Pro Phe Ser Ala Leu Asp Ile His Leu Ser		
	850	855	860
	Asp His Leu Met Gln Ala Gly Ile Leu Glu Leu Leu Arg Asp Asp Lys		
40	865	870	875
	Arg Thr Val Val Leu Val Thr His Lys Leu Gln Tyr Leu Pro His Ala		
	885	890	895
45	Asp Trp Ile Ile Ala Met Lys Asp Gly Thr Ile Gln Arg Glu Gly Thr		
	900	905	910
	Leu Lys Asp Phe Gln Arg Ser Glu Cys Gln Leu Phe Glu His Trp Lys		
50	915	920	925
	Thr Leu Met Asn Arg Gln Asp Gln Glu Leu Glu Lys Glu Thr Val Thr		
	930	935	940
55	Glu Arg Lys Ala Thr Glu Pro Pro Gln Gly Leu Ser Arg Ala Met Ser		

EP 1 217 066 A1

	945	950	955	960
5	Ser Arg Asp Gly Leu Leu Gln Asp Glu Glu Glu Glu Glu Glu Ala			
	965	970	975	
10	Ala Glu Ser Glu Glu Asp Asp Asn Leu Ser Ser Met Leu His Gln Arg			
	980	985	990	
15	Ala Glu Ile Pro Trp Arg Ala Cys Ala Lys Tyr Leu Ser Ser Ala Gly			
	995	1000	1005	
20	Ile Leu Leu Leu Ser Leu Leu Val Phe Ser Gln Leu Leu Lys His Met			
	1010	1015	1020	
25	Val Leu Val Ala Ile Asp Tyr Trp Leu Ala Lys Trp Thr Asp Ser Ala			
	1025	1030	1035	1040
30	Leu Thr Leu Thr Pro Ala Ala Arg Asn Cys Ser Leu Ser Gln Glu Cys			
	1045	1050	1055	
35	Thr Leu Asp Gln Thr Val Tyr Ala Met Val Phe Thr Val Leu Cys Ser			
	1060	1065	1070	
40	Leu Gly Ile Val Leu Cys Leu Val Thr Ser Val Thr Val Glu Trp Thr			
	1075	1080	1085	
45	Gly Leu Lys Val Ala Lys Arg Leu His Arg Ser Leu Leu Asn Arg Ile			
	1090	1095	1100	
50	Ile Leu Ala Pro Met Arg Phe Phe Glu Thr Thr Pro Leu Gly Ser Ile			
	1105	1110	1115	1120
55	Leu Asn Arg Phe Ser Ser Asp Cys Asn Thr Ile Asp Gln His Ile Pro			
	1125	1130	1135	
60	Ser Thr Leu Glu Cys Leu Ser Arg Ser Thr Leu Leu Cys Val Ser Ala			
	1140	1145	1150	
65	Leu Ala Val Ile Ser Tyr Val Thr Pro Val Phe Leu Val Ala Leu Leu			
	1155	1160	1165	
70	Pro Leu Ala Val Val Cys Tyr Phe Ile Gln Lys Tyr Phe Arg Val Ala			
	1170	1175	1180	
75	Ser Arg Asp Leu Gln Gln Leu Asp Asp Thr Thr Gln Leu Pro Leu Leu			
	1185	1190	1195	1200
80	Ser His Phe Ala Glu Thr Val Glu Gly Leu Thr Thr Ile Arg Ala Phe			

EP 1 217 066 A1

1205

1210

1215

Arg Tyr Glu Ala Arg Phe Gln Gln Lys Leu Leu Glu Tyr Thr Asp Ser
 1220 1225 1230

1220

1225

1230

Asn Asn Ile Ala Ser Leu Phe Leu Thr Ala Ala Asn Arg Trp Leu Glu
1235 1240 1245

1235

1240

1245

Val Arg Met Glu Tyr Ile Gly Ala Cys Val Val Leu Ile Ala Ala Val
1250 1255 1260

1250

1255

1260

Thr	Ser	Ile	Ser	Asn	Ser	Leu	His	Arg	Glu	Leu	Ser	Ala	Gly	Leu	Val
1265					1270					1275					1280

Gly Leu Gly Leu Thr Tyr Ala Leu Met Val Ser Asn Tyr Leu Asn Trp
1285 1290 1295

Met Val Arg Asn Leu Ala Asp Met Glu Leu Gln Leu Gly Ala Val Lys
1300 1305 1310

Arg Ile His Gly Leu Leu Lys Thr Glu Ala Glu Ser Tyr Glu Gly Leu
1315 1320 1325

Leu Ala Pro Ser Leu Ile Pro Lys Asn Trp Pro Asp Gln Gly Lys Ile
1330 1335 1340

Gln Ile Gln Asn Leu Ser Val Arg Tyr Asp Ser Ser Leu Lys Pro Val
1345 1350 1355 1360

Leu Lys His Val Asn Ala Leu Ile Ser Pro Gly Gln Lys Ile Gly Ile
1365 1370 1375

Cys Gly Arg Thr Gly Ser Gly Lys Ser Ser Phe Ser Leu Ala Phe Phe
 1380 1385 1390

Arg Met Val Asp Thr Phe Glu Gly His Ile Ile Ile Asp Gly Ile Asp
1395 1400 1405

Ile Arg Lys Leu Pro Leu His Thr Leu Pro Ser Arg Leu Ser Ile Ile
1410 1415 1420

Leu Gln Asp Pro Val Leu Phe Ser Gly Thr Ile Arg Phe Asn Leu Asp
1425 1430 1435 1440

Pro Glu Arg Lys Cys Ser Asp Ser Thr Leu Trp Glu Ala Leu Glu Ile
1445 1450 1455

Ala Gln Leu Lys Leu Val Val Lys Ala Leu Pro Gly Gly Leu Asp Ala

EP 1 217 066 A1

	1460	1465	1470
5	Ile Ile Thr Glu Gly Gly Glu Asn Phe Ser Gln Gly Gln Arg Gln Leu 1475 1480 1485		
10	Phe Cys Leu Ala Arg Ala Phe Val Arg Lys Thr Ser Ile Phe Ile Met 1490 1495 1500		
15	Asp Glu Ala Thr Ala Ser Ile Asp Met Ala Thr Glu Asn Ile Leu Gln 1505 1510 1515 1520		
20	Lys Val Val Met Thr Ala Phe Ala Asp Arg Thr Val Val Thr Ile Ala 1525 1530 1535		
25	His Arg Val His Thr Ile Leu Ser Ala Asp Leu Val Ile Val Leu Lys 1540 1545 1550		
30	Arg Gly Ala Ile Leu Glu Phe Asp Lys Pro Glu Lys Leu Leu Ser Arg 1555 1560 1565		
35	Lys Asp Ser Val Phe Ala Ser Phe Val Arg Ala Asp Lys 1570 1575 1580		
40	<210> 68 <211> 1549 <212> PRT <213> Homo sapiens		
45	<400> 68 Met Ser Leu Ser Phe Cys Gly Asn Asn Ile Ser Ser Tyr Asn Ile Asn 1 5 10 15 Asp Gly Val Leu Gln Asn Ser Cys Phe Val Asp Ala Leu Asn Leu Val 20 25 30		
50	Pro His Val Phe Leu Leu Phe Ile Thr Phe Pro Ile Leu Phe Ile Gly 35 40 45 Trp Gly Ser Gln Ser Ser Lys Val Gln Ile His His Asn Thr Trp Leu 50 55 60		
55	His Phe Pro Gly His Asn Leu Arg Trp Ile Leu Thr Phe Ala Leu Leu 65 70 75 80 Phe Val His Val Cys Glu Ile Ala Glu Gly Ile Val Ser Asp Ser Arg 85 90 95		

EP 1 217 066 A1

Arg Glu Ser Arg His Leu His Leu Phe Met Pro Ala Val Met Gly Phe
100 105 110

5 Val Ala Thr Thr Ser Ile Val Tyr Tyr His Asn Ile Glu Thr Ser
115 120 125

10 Asn Phe Pro Lys Leu Leu Ala Leu Phe Leu Tyr Trp Val Met Ala
130 135 140

15 Phe Ile Thr Lys Thr Ile Lys Leu Val Lys Tyr Cys Gln Ser Gly Leu
145 150 155 160

19 Asp Ile Ser Asn Leu Arg Phe Cys Ile Thr Gly Met Met Val Ile Leu
165 170 175

20 Asn Gly Leu Leu Met Ala Val Glu Ile Asn Val Ile Arg Val Arg Arg
180 185 190

25 Tyr Val Phe Phe Met Asn Pro Gln Lys Val Lys Pro Pro Glu Asp Leu
195 200 205

Gln Asp Leu Gly Val Arg Phe Leu Gln Pro Phe Val Asn Leu Leu Ser
210 215 220

30 Lys Ala Thr Tyr Trp Trp Met Asn Thr Leu Ile Ile Ser Ala His Lys
225 230 235 240

35 Lys Pro Ile Asp Leu Lys Ala Ile Gly Lys Leu Pro Ile Ala Met Arg
245 250 255

40 Ala Val Thr Asn Tyr Val Cys Leu Lys Asp Ala Tyr Glu Glu Gln Lys
260 265 270

45 Lys Lys Val Ala Asp His Pro Asn Arg Thr Pro Ser Ile Trp Leu Ala
275 280 285

Tyr Arg Ala Phe Gly Arg Pro Ile Leu Leu Ser Ser Thr Phe Arg
290 295 300

50 Tyr Leu Ala Asp Leu Leu Gly Phe Ala Gly Pro Leu Cys Ile Ser Gly
305 310 315 320

Ile Val Gln Arg Val Asn Glu Thr Gln Asn Gly Thr Asn Asn Thr Thr
325 330 335

55 Gly Ile Ser Glu Thr Leu Ser Ser Lys Glu Phe Leu Glu Asn Ala Tyr
340 345 350

EP 1217066 A1

Val Leu Ala Val Leu Leu Phe Leu Ala Leu Ile Leu Gln Arg Thr Phe
355 360 365

5 Leu Gln Ala Ser Tyr Tyr Val Thr Ile Glu Thr Gly Ile Asn Leu Arg
370 375 380

10 Gly Ala Leu Leu Ala Met Ile Tyr Asn Lys Ile Leu Arg Leu Ser Thr
385 390 395 400

Ser Asn Leu Ser Met Gly Glu Met Thr Leu Gly Gln Ile Asn Asn Leu
405 410 415

15 Val Ala Ile Glu Thr Asn Gln Leu Met Trp Phe Leu Phe Leu Cys Pro
420 425 430

20 Asn Leu Trp Ala Met Pro Val Gln Ile Ile Met Gly Val Ile Leu Leu
435 440 445

Tyr Asn Leu Leu Gly Ser Ser Ala Leu Val Gly Ala Ala Val Ile Val
25 450 455 460

Leu Leu Ala Pro Ile Gln Tyr Phe Ile Ala Thr Lys Leu Ala Glu Ala
465 470 475 480

30 Gln Lys Ser Thr Leu Asp Tyr Ser Thr Glu Arg Leu Lys Lys Thr Asn
485 490 495

Glu Ile Leu Lys Gly Ile Lys Leu Leu Lys Leu Tyr Ala Trp Glu His
35 500 505 510

Ile Phe Cys Lys Ser Val Glu Glu Thr Arg Met Lys Glu Leu Ser Ser
515 520 525

40 Leu Lys Thr Phe Ala Leu Tyr Thr Ser Leu Ser Ile Phe Met Asn Ala
530 535 540

45 Ala Ile Pro Ile Ala Ala Val Leu Ala Thr Phe Val Thr His Ala Tyr
545 550 555 560

Ala Ser Gly Asn Asn Leu Lys Pro Ala Glu Ala Phe Ala Ser Leu Ser
565 570 575

50 Leu Phe His Ile Leu Val Thr Pro Leu Ser Leu Leu Phe Thr Val Val
580 585 590

55 Arg Phe Ala Val Lys Ala Ile Ile Ser Val Gln Lys Leu Asn Glu Phe
595 600 605

EP 1217 066 A1

Leu Leu Ser Asp Glu Ile Gly Asp Asp Ser Trp Arg Thr Gly Glu Ser
 610 615 620

5 Ser Leu Pro Phe Glu Ser Cys Lys Lys His Thr Gly Val Gln Pro Lys
 625 630 635 640

10 Thr Ile Asn Arg Lys Gln Pro Gly Arg Tyr His Leu Asp Ser Tyr Glu
 645 650 655

15 Gln Ser Thr Arg Arg Leu Arg Pro Ala Glu Thr Glu Asp Ile Ala Ile
 660 665 670

20 Lys Val Thr Asn Gly Tyr Phe Ser Trp Gly Ser Gly Leu Ala Thr Leu
 675 680 685

25 Ser Asn Ile Asp Ile Arg Ile Pro Thr Gly Gln Leu Thr Met Ile Val
 690 695 700

Gly Gln Val Gly Cys Gly Lys Ser Ser Leu Leu Leu Ala Ile Leu Gly
 705 710 715 720

30 Glu Met Gln Thr Leu Glu Gly Lys Val His Trp Ser Asn Val Asn Glu
 725 730 735

35 Ser Glu Pro Ser Phe Glu Ala Thr Arg Ser Arg Asn Arg Tyr Ser Val
 740 745 750

Ala Tyr Ala Ala Gln Lys Pro Trp Leu Leu Asn Ala Thr Val Glu Glu
 755 760 765

40 Asn Ile Thr Phe Gly Ser Pro Phe Asn Lys Gln Arg Tyr Lys Ala Val
 770 775 780

45 Thr Asp Ala Cys Ser Leu Gln Pro Asp Ile Asp Leu Leu Pro Phe Gly
 785 790 795 800

Arg Gln Arg Ile Cys Val Ala Arg Ala Leu Tyr Gln Asn Thr Asn Ile
 820 825 830

50 Val Phe Leu Asp Asp Pro Phe Ser Ala Leu Asp Ile His Leu Ser Asp
 835 840

55 His Leu Met Gln Glu Gly Ile Leu Lys Phe Leu Gln Asp Asp Lys Arg
 850 855 860

EP 1 217 066 A1

	Thr Leu Val Leu Val Thr His Lys Leu Gln Tyr Leu Thr His Ala Asp			
865	870	875	880	
5	Trp Ile Ile Ala Met Lys Asp Gly Ser Val Leu Arg Glu Gly Thr Leu			
	885	890	895	
10	Lys Asp Ile Gln Thr Lys Asp Val Glu Leu Tyr Glu His Trp Lys Thr			
	900	905	910	
15	Leu Met Asn Arg Gln Asp Gln Glu Leu Glu Lys Asp Met Glu Ala Asp			
	915	920	925	
Gln Thr Thr Leu Glu Arg Lys Thr Leu Arg Arg Ala Met Tyr Ser Arg				
930	935	940		
20	Glu Ala Lys Ala Gln Met Glu Asp Glu Asp Glu Glu Glu Glu Glu			
	945	950	955	960
25	Glu Asp Glu Asp Asp Asn Met Ser Thr Val Met Arg Leu Arg Thr Lys			
	965	970	975	
Met Pro Trp Lys Thr Cys Trp Arg Tyr Leu Thr Ser Gly Gly Phe Phe				
980	985	990		
30	Leu Leu Ile Leu Met Ile Phe Ser Lys Leu Leu Lys His Ser Val Ile			
	995	1000	1005	
35	Val Ala Ile Asp Tyr Trp Leu Ala Thr Trp Thr Ser Glu Tyr Ser Ile			
	1010	1015	1020	
Asn Asn Thr Gly Lys Ala Asp Gln Thr Tyr Tyr Val Ala Gly Phe Ser				
1025	1030	1035	1040	
40	Ile Leu Cys Gly Ala Gly Ile Phe Leu Cys Leu Val Thr Ser Leu Thr			
	1045	1050	1055	
Val Glu Trp Met Gly Leu Thr Ala Ala Lys Asn Leu His His Asn Leu				
45	1060	1065	1070	
Leu Asn Lys Ile Ile Leu Gly Pro Ile Arg Phe Phe Asp Thr Thr Pro				
	1075	1080	1085	
50	Leu Gly Leu Ile Leu Asn Arg Phe Ser Ala Asp Thr Asn Ile Ile Asp			
	1090	1095	1100	
55	Gln His Ile Pro Pro Thr Leu Glu Ser Leu Thr Arg Ser Thr Leu Leu			
	1105	1110	1115	1120

EP 1 217 066 A1

Cys Leu Ser Ala Ile Gly Met Ile Ser Tyr Ala Thr Pro Val Phe Leu
 1125 1130 1135
 5 Val Ala Leu Leu Pro Leu Gly Val Ala Phe Tyr Phe Ile Gln Lys Tyr
 1140 1145 1150
 10 Phe Arg Val Ala Ser Lys Asp Leu Gln Glu Leu Asp Asp Ser Thr Gln
 1155 1160 1165
 15 Leu Pro Leu Leu Cys His Phe Ser Glu Thr Ala Glu Gly Leu Thr Thr
 1170 1175 1180
 20 Ile Arg Ala Phe Arg His Glu Thr Arg Phe Lys Gln Arg Met Leu Glu
 1185 1190 1195 1200
 25 Leu Thr Asp Thr Asn Asn Ile Ala Tyr Leu Phe Leu Ser Ala Ala Asn
 1205 1210 1215
 30 Arg Trp Leu Glu Val Arg Thr Asp Tyr Leu Gly Ala Cys Ile Val Leu
 1220 1225 1230
 35 Thr Ala Ser Ile Ala Ser Ile Ser Gly Ser Ser Asn Ser Gly Leu Val
 1235 1240 1245
 40 Gly Leu Gly Leu Leu Tyr Ala Leu Thr Ile Thr Asn Tyr Leu Asn Trp
 1250 1255 1260
 45 Val Val Arg Asn Leu Ala Asp Leu Glu Val Gln Met Gly Ala Val Lys
 1265 1270 1275 1280
 50 Lys Val Asn Ser Phe Leu Thr Met Glu Ser Glu Asn Tyr Glu Gly Thr
 1285 1290 1295
 55 Met Asp Pro Ser Gln Val Pro Glu His Trp Pro Gln Glu Gly Glu Ile
 1300 1305 1310
 60 Lys Ile His Asp Leu Cys Val Arg Tyr Glu Asn Asn Leu Lys Pro Val
 1315 1320 1325
 65 Leu Lys His Val Lys Ala Tyr Ile Lys Pro Gly Gln Lys Val Gly Ile
 1330 1335 1340
 70 Cys Gly Arg Thr Gly Ser Gly Lys Ser Ser Leu Ser Leu Ala Phe Phe
 1345 1350 1355 1360
 75 Arg Met Val Asp Ile Phe Asp Gly Lys Ile Val Ile Asp Gly Ile Asp
 1365 1370 1375

EP 1 217 066 A1

Ile Ser Lys Leu Pro Leu His Thr Leu Arg Ser Arg Leu Ser Ile Ile
1380 1385 1390

5 Leu Gln Asp Pro Ile Leu Phe Ser Gly Ser Ile Arg Phe Asn Leu Asp
1395 1400 1405

10 Pro Glu Cys Lys Cys Thr Asp Asp Arg Leu Trp Glu Ala Leu Glu Ile
1410 1415 1420

15 Ala Gln Leu Lys Asn Met Val Lys Ser Leu Pro Gly Gly Leu Asp Ala
1425 1430 1435 1440

Val Val Thr Glu Gly Gly Glu Asn Phe Ser Val Gly Gln Arg Gln Leu
1445 1450 1455

20 Phe Cys Leu Ala Arg Ala Phe Val Arg Lys Ser Ser Ile Leu Ile Met
1460 1465 1470

25 Asp Glu Ala Thr Ala Ser Ile Asp Met Ala Thr Glu Asn Ile Leu Gln
1475 1480 1485

Lys Val Val Met Thr Ala Phe Ala Asp Arg Thr Val Val Thr Met Ala
1490 1495 1500

30 His Arg Val Ser Ser Ile Met Asp Ala Gly Leu Val Leu Val Phe Ser
1505 1510 1515 1520

35 Glu Gly Ile Leu Val Glu Cys Asp Thr Val Pro Asn Leu Phe Ala His
1525 1530 1535

40 Lys Asn Gly Pro Phe Ser Thr Leu Val Met Thr Asn Lys
1540 1545

45 <210> 69
 <211> 1513
 <212> PRT
 <213> Homo sapiens

50 <400> 69
 Gly Ser Gly Cys Leu Gly Ala Glu Lys Arg Glu Gly Lys Asn Arg Trp
 1 5 10 15

55 Gln Gly Glu Ala Ser Met Glu Arg Leu Leu Ala Gln Leu Cys Gly Ser
 20 25 30

EP 1217 066 A1

Ser Ala Ala Trp Pro Leu Pro Leu Trp Glu Gly Asp Thr Thr Gly His
35 40 45

5 Cys Phe Thr Gln Leu Val Leu Ser Ala Leu Pro His Ala Leu Leu Ala
50 55 60

10 Val Leu Ser Ala Cys Tyr Leu Gly Thr Pro Arg Ser Pro Asp Tyr Ile
65 70 75 80

Leu Pro Cys Ser Pro Gly Trp Arg Leu Arg Leu Ala Ala Ser Phe Leu
15 85 90 95

15 Leu Ser Val Phe Pro Leu Leu Asp Leu Leu Pro Val Ala Leu Pro Pro
100 105 110

20 Gly Ala Gly Pro Gly Pro Ile Gly Leu Glu Val Leu Ala Gly Cys Val
115 120 125

Ala Ala Val Ala Trp Ile Ser His Ser Leu Ala Leu Trp Val Leu Ala
25 130 135 140

His Ser Pro His Gly His Ser Arg Gly Pro Leu Ala Leu Ala Leu Val
145 150 155 160

30 Ala Leu Leu Pro Ala Pro Ala Leu Val Leu Thr Val Leu Trp His Cys
165 170 175

Gln Arg Gly Thr Leu Leu Pro Pro Leu Leu Pro Gly Pro Met Ala Arg
35 180 185 190

Leu Cys Leu Leu Ile Leu Gln Leu Ala Ala Leu Leu Ala Tyr Ala Leu
195 200 205

40 Gly Trp Ala Ala Pro Gly Gly Pro Arg Glu Pro Trp Ala Gln Glu Pro
210 215 220

Leu Leu Pro Glu Asp Gln Glu Pro Glu Val Ala Glu Asp Gly Glu Ser
45 225 230 235 240

Trp Leu Ser Arg Phe Ser Tyr Ala Trp Leu Ala Pro Leu Leu Ala Arg
245 250 255

50 Gly Ala Cys Gly Glu Leu Arg Gln Pro Gln Asp Ile Cys Arg Leu Pro
260 265 270

His Arg Leu Gln Pro Thr Tyr Leu Ala Arg Val Phe Gln Ala His Trp
55 275 280 285

EP 1 217 066 A1

Gln Glu Gly Ala Arg Leu Trp Arg Ala Leu Tyr Gly Ala Phe Gly Arg
290 295 300

5 Cys Tyr Leu Ala Leu Gly Leu Leu Lys Leu Val Gly Thr Met Leu Gly
305 310 315 320

10 Phe Ser Gly Pro Leu Leu Leu Ser Leu Leu Val Gly Phe Leu Glu Glu
325 330 335

Gly Gln Glu Pro Leu Ser His Gly Leu Leu Tyr Ala Leu Gly Leu Ala
340 345 350

15 Gly Gly Ala Val Leu Gly Ala Val Leu Gln Asn Gln Tyr Gly Tyr Glu
355 360 365

20 Val Tyr Lys Val Thr Leu Gln Ala Arg Gly Ala Val Leu Asn Ile Leu
370 375 380

Tyr Cys Lys Ala Leu Gln Leu Gly Pro Ser Arg Pro Pro Thr Gly Glu
25 385 390 395 400

Ala Leu Asn Leu Leu Gly Thr Asp Ser Glu Arg Leu Leu Asn Phe Ala
405 410 415

30 Gly Ser Phe His Glu Ala Trp Gly Leu Pro Leu Gln Leu Ala Ile Thr
420 425 430

Leu Tyr Leu Leu Tyr Gln Gln Val Gly Val Ala Phe Val Gly Gly Leu
35 435 440 445

Ile Leu Ala Leu Leu Val Pro Val Asn Lys Val Ile Ala Thr Arg
450 455 460

40 Ile Met Ala Ser Asn Gln Glu Met Leu Gln His Lys Asp Ala Arg Val
465 470 475 480

Lys Leu Val Thr Glu Leu Leu Ser Gly Ile Arg Val Ile Lys Phe Cys
45 485 490 495

Gly Trp Glu Gln Ala Leu Gly Ala Arg Val Glu Ala Cys Arg Ala Arg
500 505 510

50 Glu Leu Gly Arg Leu Arg Val Ile Lys Tyr Leu Asp Ala Ala Cys Val
515 520 525

55 Tyr Leu Trp Ala Ala Leu Pro Val Val Ile Ser Ile Val Ile Phe Ile
530 535 540

EP 1 217 066 A1

Thr Tyr Val Leu Met Gly His Gln Leu Thr Ala Thr Lys Val Phe Thr
545 550 555 560

5 Ala Leu Ala Leu Val Arg Met Leu Ile Leu Pro Leu Asn Asn Phe Pro
565 570 575

10 Trp Val Ile Asn Gly Leu Leu Glu Ala Lys Val Ser Leu Asp Arg Ile
580 585 590

Gln Leu Phe Leu Asp Leu Pro Asn His Asn Pro Gln Ala Tyr Tyr Ser
595 600 605

15 Pro Asp Pro Pro Ala Glu Pro Ser Thr Val Leu Glu Leu His Gly Ala
610 615 620

20 Leu Phe Ser Trp Asp Pro Val Gly Thr Ser Leu Glu Thr Phe Ile Ser
625 630 635 640

His Leu Glu Val Lys Lys Gly Met Leu Val Gly Ile Val Gly Lys Val
25 645 650 655

Gly Cys Gly Lys Ser Ser Leu Leu Ala Ala Ile Ala Gly Glu Leu His
660 665 670

30 Arg Leu Arg Gly His Val Ala Val Arg Gly Leu Ser Lys Gly Phe Gly
675 680 685

Leu Ala Thr Gln Glu Pro Trp Ile Gln Phe Ala Thr Ile Arg Asp Asn
35 690 695 700

Ile Leu Phe Gly Lys Thr Phe Asp Ala Gln Leu Tyr Lys Glu Val Leu
705 710 715 720

40 Glu Ala Cys Ala Leu Asn Asp Asp Leu Ser Ile Leu Pro Ala Gly Asp
725 730 735

Gln Thr Glu Val Gly Glu Lys Gly Val Thr Leu Ser Gly Gly Gln Arg
45 740 745 750

Ala Arg Ile Ala Leu Ala Arg Ala Val Tyr Gln Glu Lys Glu Leu Tyr
755 760 765

50 Leu Leu Asp Asp Pro Leu Ala Ala Val Asp Ala Asp Val Ala Asn His
770 775 780

55 Leu Leu His Arg Cys Ile Leu Gly Met Leu Ser Tyr Thr Thr Arg Leu
785 790 795 800

EP 1 217 066 A1

Leu Cys Thr His Arg Thr Glu Tyr Leu Glu Arg Ala Asp Ala Val Leu
 805 810 815

5 Leu Met Glu Ala Gly Arg Leu Ile Arg Ala Gly Pro Pro Ser Glu Ile
 820 825 830

10 Leu Pro Leu Val Gln Ala Val Pro Lys Ala Trp Ala Glu Asn Gly Gln
 835 840 845

15 Glu Ser Asp Ser Ala Thr Ala Gln Ser Val Gln Asn Pro Glu Lys Thr
 850 855 860

20 Lys Glu Gly Leu Glu Glu Gln Ser Thr Ser Gly Arg Leu Leu Gln
 865 870 875 880

25 Glu Glu Ser Lys Lys Glu Gly Ala Val Ala Leu His Val Tyr Gln Ala
 885 890 895

30 Tyr Trp Lys Ala Val Gly Gln Gly Leu Ala Leu Ala Ile Leu Phe Ser
 900 905 910

35 Leu Leu Leu Met Gln Ala Thr Arg Asn Ala Ala Asp Trp Trp Leu Ser
 915 920 925

40 His Trp Ile Ser Gln Leu Lys Ala Glu Asn Ser Ser Gln Glu Ala Gln
 930 935 940

45 Pro Ser Thr Ser Pro Ala Ser Met Gly Leu Phe Ser Pro Gln Leu Leu
 945 950 955 960

50 Leu Phe Ser Pro Gly Asn Leu Tyr Ile Pro Val Phe Pro Leu Pro Lys
 965 970 975

55 Ala Ala Pro Asn Gly Ser Ser Asp Ile Arg Phe Tyr Leu Thr Val Tyr
 980 985 990

60 Ala Thr Ile Ala Gly Val Asn Ser Leu Cys Thr Leu Leu Arg Ala Val
 995 1000 1005

65 Leu Phe Ala Ala Gly Thr Leu Gln Ala Ala Ala Thr Leu His Arg Arg
 1010 1015 1020

70 Leu Leu His Arg Val Leu Met Ala Pro Val Thr Phe Phe Asn Ala Thr
 1025 1030 1035 1040

75 Pro Thr Gly Arg Ile Leu Asn Arg Phe Ser Ser Asp Val Ala Cys Ala
 1045 1050 1055

EP 1 217 066 A1

Asp Asp Ser Leu Pro Phe Ile Leu Asn Ile Leu Leu Ala Asn Ala Ala
 1060 1065 1070

5 Gly Leu Leu Gly Leu Leu Ala Val Leu Gly Ser Gly Leu Pro Trp Leu
 1075 1080 1085

10 Leu Leu Leu Leu Pro Pro Leu Ser Ile Met Tyr Tyr His Val Gln Arg
 1090 1095 1100

15 His Tyr Arg Ala Ser Ser Arg Glu Leu Arg Arg Leu Gly Ser Leu Thr
 1105 1110 1115 1120

20 Leu Ser Pro Leu Tyr Ser His Leu Ala Asp Thr Leu Ala Gly Leu Ser
 1125 1130 1135

25 Val Leu Arg Ala Thr Gly Ala Thr Tyr Arg Phe Glu Glu Glu Asn Leu
 1140 1145 1150

Arg Leu Leu Glu Leu Asn Gln Arg Cys Gln Phe Ala Thr Ser Ala Thr
 1155 1160 1165

30 Met Gln Trp Leu Asp Ile Arg Leu Gln Leu Met Gly Ala Ala Val Val
 1170 1175 1180

35 Ser Ala Ile Ala Gly Ile Ala Leu Val Gln His Gln Gln Gly Leu Ala
 1185 1190 1195 1200

Asn Pro Gly Leu Val Gly Leu Ser Leu Ser Tyr Ala Leu Ser Leu Thr
 1205 1210 1215

40 Gly Leu Leu Ser Gly Leu Val Ser Ser Phe Thr Gln Thr Glu Ala Met
 1220 1225 1230

45 Leu Val Ser Val Glu Arg Leu Glu Glu Tyr Thr Cys Asp Leu Pro Gln
 1235 1240 1245

Glu Pro Gln Gly Gln Pro Leu Gln Leu Gly Thr Gly Trp Leu Thr Gln
 1250 1255 1260

50 Gly Gly Val Glu Phe Gln Asp Val Val Leu Ala Tyr Arg Pro Gly Leu
 1265 1270 1275 1280

Pro Asn Ala Leu Asp Gly Val Thr Phe Cys Val Gln Pro Gly Glu Lys
 1285 1290 1295

55 Leu Gly Ile Val Gly Arg Thr Gly Ser Gly Lys Ser Ser Leu Leu Leu
 1300 1305 1310

EP 1 217 066 A1

Val Leu Phe Arg Leu Leu Glu Pro Ser Ser Gly Arg Val Leu Leu Asp
1315 1320 1325

5 Gly Val Asp Thr Ser Gln Leu Glu Leu Ala Gln Leu Arg Ser Gln Leu
1330 1335 1340

Ala Ile Ile Pro Gln Glu Pro Phe Leu Phe Ser Gly Thr Val Arg Glu
10 1345 1350 1355 1360

Asn Leu Asp Pro Gln Gly Leu His Lys Asp Arg Ala Leu Trp Gln Ala
1365 1370 1375

15 Leu Lys Gln Cys His Leu Ser Glu Val Ile Thr Ser Met Gly Gly Leu
1380 1385 1390

Asp Gly Glu Leu Gly Glu Gly Arg Ser Leu Ser Leu Gly Gln Arg
20 1395 1400 1405

Gln Leu Leu Cys Leu Ala Arg Ala Leu Leu Thr Asp Ala Lys Ile Leu
1410 1415 1420

25 Cys Ile Asp Glu Ala Thr Ala Ser Val Asp Gln Lys Thr Asp Gln Leu
1425 1430 1435 1440

Leu Gln Gln Thr Ile Cys Lys Arg Phe Ala Asn Lys Thr Val Leu Thr
30 1445 1450 1455

Ile Ala His Arg Leu Asn Thr Ile Leu Asn Ser Asp Arg Val Leu Val
1460 1465 1470

35 Leu Gln Ala Gly Arg Val Val Glu Leu Asp Ser Pro Ala Thr Leu Arg
1475 1480 1485

40 Asn Gln Pro His Ser Leu Phe Gln Gln Leu Leu Gln Ser Ser Gln Gln
1490 1495 1500

Gly Val Pro Ala Ser Leu Gly Gly Pro
45 1505 1510

<210> 70
50 <211> 745
<212> PRT
<213> Homo sapiens

<400> 70
55 Met Pro Val Leu Ser Arg Pro Arg Pro Trp Arg Gly Asn Thr Leu Lys

EP 1 217 066 A1

	1	5	10	15
5	Arg Thr Ala Val Leu Leu Ala Leu Ala Ala Tyr Gly Ala His Lys Val			
	20	25	30	
	Tyr Pro Leu Val Arg Gln Cys Leu Ala Pro Ala Arg Gly Leu Gln Ala			
	35	40	45	
10	Pro Ala Gly Glu Pro Thr Gln Glu Ala Ser Gly Val Ala Ala Ala Lys			
	50	55	60	
15	Ala Gly Met Asn Arg Val Phe Leu Gln Arg Leu Leu Trp Leu Leu Arg			
	65	70	75	80
	Leu Leu Phe Pro Arg Val Leu Cys Arg Glu Thr Gly Leu Leu Ala Leu			
	85	90	95	
20	His Ser Ala Ala Leu Val Ser Arg Thr Phe Leu Ser Val Tyr Val Ala			
	100	105	110	
25	Arg Leu Asp Gly Arg Leu Ala Arg Cys Ile Val Arg Lys Asp Pro Arg			
	115	120	125	
	Ala Phe Gly Trp Gln Leu Leu Gln Trp Leu Leu Ile Ala Leu Pro Ala			
30	130	135	140	
	Thr Phe Val Asn Ser Ala Ile Arg Tyr Leu Glu Gly Gln Leu Ala Leu			
	145	150	155	160
35	Ser Phe Arg Ser Arg Leu Val Ala His Ala Tyr Arg Leu Tyr Phe Ser			
	165	170	175	
	Gln Gln Thr Tyr Arg Val Ser Asn Met Asp Gly Arg Leu Arg Asn			
40	180	185	190	
	Pro Asp Gln Ser Leu Thr Glu Asp Val Val Ala Phe Ala Ala Ser Val			
	195	200	205	
45	Ala His Leu Tyr Ser Asn Leu Thr Lys Pro Leu Leu Asp Val Ala Val			
	210	215	220	
	Thr Ser Tyr Thr Leu Leu Arg Ala Ala Arg Ser Arg Gly Ala Gly Thr			
50	225	230	235	240
	Ala Trp Pro Ser Ala Ile Ala Gly Leu Val Val Phe Leu Thr Ala Asn			
	245	250	255	
55	Val Leu Arg Ala Phe Ser Pro Lys Phe Gly Glu Leu Val Ala Glu Glu			

EP 1 217 066 A1

	260	265	270
5	Ala Arg Arg Lys Gly Glu Leu Arg Tyr Met His Ser Arg Val Val Ala 275	280	285
10	Asn Ser Glu Glu Ile Ala Phe Tyr Gly Gly His Glu Val Glu Leu Ala 290	295	300
15	Leu Leu Gln Arg Ser Tyr Gln Asp Leu Ala Ser Gln Ile Asn Leu Ile 305	310	315
20	Leu Leu Glu Arg Leu Trp Tyr Val Met Leu Glu Gln Phe Leu Met Lys 325	330	335
25	Tyr Val Trp Ser Ala Ser Gly Leu Leu Met Val Ala Val Pro Ile Ile 340	345	350
30	Thr Ala Thr Gly Tyr Ser Glu Ser Asp Ala Glu Ala Val Lys Lys Ala 355	360	365
35	Ala Leu Glu Lys Lys Glu Glu Leu Val Ser Glu Arg Thr Glu Ala 370	375	380
40	Phe Thr Ile Ala Arg Asn Leu Leu Thr Ala Ala Ala Asp Ala Ile Glu 385	390	395
45	Arg Ile Met Ser Ser Tyr Lys Glu Val Thr Glu Leu Ala Gly Tyr Thr 405	410	415
50	Ala Arg Val His Glu Met Phe Gln Val Phe Glu Asp Val Gln Arg Cys 420	425	430
55	His Phe Lys Arg Pro Arg Glu Leu Glu Asp Ala Gln Ala Gly Ser Gly 435	440	445
60	Thr Ile Gly Arg Ser Gly Val Arg Val Glu Gly Pro Leu Lys Ile Arg 450	455	460
65	Gly Gln Val Val Asp Val Glu Gln Gly Ile Ile Cys Glu Asn Ile Pro 465	470	475
70	Ile Val Thr Pro Ser Gly Glu Val Val Ala Ser Leu Asn Ile Arg 485	490	495
75	Val Glu Glu Gly Met His Leu Leu Ile Thr Gly Pro Asn Gly Cys Gly 500	505	510
80	Lys Ser Ser Leu Phe Arg Ile Leu Gly Gly Leu Trp Pro Thr Tyr Gly		

EP 1 217 066 A1

	515	520	525
5	Gly Val Leu Tyr Lys Pro Pro Pro Gln Arg Met Phe Tyr Ile Pro Gln 530	535	540
10	Arg Pro Tyr Met Ser Val Gly Ser Leu Arg Asp Gln Val Ile Tyr Pro 545	550	555
	Asp Ser Val Glu Asp Met Gln Arg Lys Gly Tyr Ser Glu Gln Asp Leu 565	570	575
15	Glu Ala Ile Leu Asp Val Val His Leu His His Ile Leu Gln Arg Glu 580	585	590
20	Gly Gly Trp Glu Ala Met Cys Asp Trp Lys Asp Val Leu Ser Gly Gly 595	600	605
	Glu Lys Gln Arg Ile Gly Met Ala Arg Met Phe Tyr His Arg Pro Lys 610	615	620
25	Tyr Ala Leu Leu Asp Glu Cys Thr Ser Ala Val Ser Ile Asp Val Glu 625	630	635
	Gly Lys Ile Phe Gln Ala Ala Lys Asp Ala Gly Ile Ala Leu Leu Ser 645	650	655
30	Ile Thr His Arg Pro Ser Leu Trp Lys Tyr His Thr His Leu Leu Gln 660	665	670
35	Phe Asp Gly Glu Gly Trp Lys Phe Glu Lys Leu Asp Ser Ala Ala 675	680	685
40	Arg Leu Ser Leu Thr Glu Glu Lys Gln Arg Leu Glu Gln Gln Leu Ala 690	695	700
	Gly Ile Pro Lys Met Gln Arg Arg Leu Gln Glu Leu Cys Gln Ile Leu 705	710	715
45	Gly Glu Ala Val Ala Pro Ala His Val Pro Ala Pro Ser Pro Gln Gly 725	730	735
	Pro Gly Gly Leu Gln Gly Ala Ser Thr 740	745	
55	<210> 71 <211> 740		

EP 1 217 066 A1

<212> PRT

<213> Homo sapiens

5

<400> 71

Met Thr His Met Leu Asn Ala Ala Ala Asp Arg Val Lys Trp Thr Arg
1 5 10 15

10

Ser Ser Ala Ala Lys Arg Ala Ala Cys Leu Val Ala Ala Ala Tyr Ala
20 25 30

15

Leu Lys Thr Leu Tyr Pro Ile Ile Gly Lys Arg Leu Lys Gln Ser Gly
35 40 45

His Gly Lys Lys Lys Ala Ala Ala Tyr Pro Ala Ala Glu Asn Thr Glu
50 55 60

20

Ile Leu His Cys Thr Glu Thr Ile Cys Glu Lys Pro Ser Pro Gly Val
65 70 75 80

25

Asn Ala Asp Phe Phe Lys Gln Leu Leu Glu Leu Arg Lys Ile Leu Phe
85 90 95

30

Pro Lys Leu Val Thr Thr Glu Thr Gly Trp Leu Cys Leu His Ser Val
100 105 110

Ala Leu Ile Ser Arg Thr Phe Leu Ser Ile Tyr Val Ala Gly Leu Asp
115 120 125

35

Gly Lys Ile Val Lys Ser Ile Val Glu Lys Lys Pro Arg Thr Phe Ile
130 135 140

40

Ile Lys Leu Ile Lys Trp Leu Met Ile Ala Ile Pro Ala Thr Phe Val
145 150 155 160

Asn Ser Ala Ile Arg Tyr Leu Glu Cys Lys Leu Ala Leu Ala Phe Arg
165 170 175

45

Thr Arg Leu Val Asp His Ala Tyr Glu Thr Tyr Phe Thr Asn Gln Thr
180 185 190

50

Tyr Tyr Lys Val Ile Asn Met Asp Gly Arg Leu Ala Asn Pro Asp Gln
195 200 205

55

Ser Leu Thr Glu Asp Ile Met Met Phe Ser Gln Ser Val Ala His Leu
210 215 220

Tyr Ser Asn Leu Thr Lys Pro Ile Leu Asp Val Met Leu Thr Ser Tyr
225 230 235 240

EP 1 217 066 A1

5	Thr Leu Ile Gln Thr Ala Thr Ser Arg Gly Ala Ser Pro Ile Gly Pro 245 250 255
10	Thr Leu Leu Ala Gly Leu Val Val Tyr Ala Thr Ala Lys Val Leu Lys 260 265 270
15	Ala Cys Ser Pro Lys Phe Gly Lys Leu Val Ala Glu Glu Ala His Arg 275 280 285
20	Lys Gly Tyr Leu Arg Tyr Val His Ser Arg Ile Ile Ala Asn Val Glu 290 295 300
25	Glu Ile Ala Phe Tyr Arg Gly His Lys Val Glu Met Lys Gln Leu Gln 305 310 315 320
30	Lys Ser Tyr Lys Ala Leu Ala Asp Gln Met Asn Leu Ile Leu Ser Lys 325 330 335
35	Arg Leu Trp Tyr Ile Met Ile Glu Gln Phe Leu Met Lys Tyr Val Trp 340 345 350
40	Ser Ser Ser Gly Leu Ile Met Val Ala Ile Pro Ile Ile Thr Ala Thr 355 360 365
45	Gly Phe Ala Asp Gly Glu Asp Gly Gln Lys Gln Val Met Val Ser Glu 370 375 380
50	Arg Thr Glu Ala Phe Thr Thr Ala Arg Asn Leu Leu Ala Ser Gly Ala 385 390 395 400
55	Asp Ala Ile Glu Arg Ile Met Ser Ser Tyr Lys Glu Val Thr Glu Leu 405 410 415
60	Ala Gly Tyr Thr Ala Arg Val Tyr Asn Met Phe Trp Val Phe Asp Glu 420 425 430
65	Val Lys Arg Gly Ile Tyr Lys Arg Thr Ala Val Ile Gln Glu Ser Glu 435 440 445
70	Ser His Ser Lys Asn Gly Ala Lys Val Glu Leu Pro Leu Ser Asp Thr 450 455 460
75	Leu Ala Ile Lys Gly Lys Val Ile Asp Val Asp His Gly Ile Ile Cys 465 470 475 480
80	Glu Asn Val Pro Ile Ile Thr Pro Ala Gly Glu Val Val Ala Ser Arg 485 490 495

EP 1 217 066 A1

	Leu Asn Phe Lys Val Glu Glu Gly Met His Leu Leu Ile Thr Gly Pro			
5	500	505	510	
	Asn Gly Cys Gly Lys Ser Ser Leu Phe Arg Ile Leu Ser Gly Leu Trp			
	515	520	525	
10	Pro Val Tyr Glu Gly Val Leu Tyr Lys Pro Pro Pro Gln His Met Phe			
	530	535	540	
15	Tyr Ile Pro Gln Arg Pro Tyr Met Ser Leu Gly Ser Leu Arg Asp Gln			
	545	550	555	560
20	Val Ile Tyr Pro Asp Ser Val Asp Asp Met His Asp Lys Gly Tyr Thr			
	565	570	575	
	Asp Gln Asp Leu Glu Arg Ile Leu His Asn Val His Leu Tyr His Ile			
	580	585	590	
25	Val Gln Arg Glu Gly Gly Trp Asp Ala Val Met Asp Trp Lys Asp Val			
	595	600	605	
	Leu Ser Gly Gly Glu Lys Gln Arg Met Gly Met Ala Arg Met Phe Tyr			
	610	615	620	
30	His Lys Pro Lys Tyr Ala Leu Leu Asp Glu Cys Thr Ser Ala Val Ser			
	625	630	635	640
35	Ile Asp Val Glu Gly Lys Ile Phe Gln Ala Ala Lys Gly Ala Gly Ile			
	645	650	655	
	Ser Leu Leu Ser Ile Thr His Arg Pro Ser Leu Trp Lys Tyr His Thr			
	660	665	670	
40	His Leu Leu Gln Phe Asp Gly Glu Gly Gly Trp Arg Phe Glu Gln Leu			
	675	680	685	
45	Asp Thr Ala Ile Arg Leu Thr Leu Ser Glu Glu Lys Gln Lys Leu Glu			
	690	695	700	
	Ser Gln Leu Ala Gly Ile Pro Lys Met Gln Gln Arg Leu Asn Glu Leu			
	705	710	715	720
50	Cys Lys Ile Leu Gly Glu Asp Ser Val Leu Lys Thr Ile Lys Asn Glu			
	725	730	735	
55	Asp Glu Thr Ser			
	740			

5 <210> 72
 <211> 659
 <212> PRT
 <213> Homo sapiens

10 <400> 72
 Met Ala Ala Phe Ser Lys Tyr Leu Thr Ala Arg Asn Ser Ser Leu Ala
 1 5 10 15

15 Gly Ala Ala Phe Leu Leu Leu Cys Leu Leu His Lys Lys Arg Arg Arg Ala
 20 25 30

20 Leu Gly Leu His Gly Lys Lys Ser Gly Lys Pro Pro Leu Gln Asn Asn
 35 40 45

25 Glu Lys Glu Gly Lys Lys Glu Arg Ala Val Val Asp Lys Val Phe Phe
 50 55 60

30 Ser Arg Leu Ile Gln Ile Leu Lys Ile Met Val Pro Arg Thr Phe Cys
 65 70 75 80

35 Lys Glu Thr Gly Tyr Leu Val Leu Ile Ala Val Met Leu Val Ser Arg
 85 90 95

40 Thr Tyr Cys Asp Val Trp Met Ile Gln Asn Gly Thr Leu Ile Glu Ser
 100 105 110

45 Gly Ile Ile Gly Arg Ser Arg Lys Asp Phe Lys Arg Tyr Leu Leu Asn
 115 120 125

50 Phe Ile Ala Ala Met Pro Leu Ile Ser Leu Val Asn Asn Phe Leu Lys
 130 135 140

55 Tyr Gly Leu Asn Glu Leu Lys Leu Cys Phe Arg Val Arg Leu Thr Lys
 145 150 155 160

60 Tyr Leu Tyr Glu Glu Tyr Leu Gln Ala Phe Thr Tyr Tyr Lys Met Gly
 165 170 175

65 Asn Leu Asp Asn Arg Ile Ala Asn Pro Asp Gln Leu Leu Thr Gln Asp
 180 185 190

70 Val Glu Lys Phe Cys Asn Ser Val Val Asp Leu Tyr Ser Asn Leu Ser
 195 200 205

EP 1 217 066 A1

Lys Pro Phe Leu Asp Ile Val Leu Tyr Ile Phe Lys Leu Thr Ser Ala
 210 215 220

5 Ile Gly Ala Gln Gly Pro Ala Ser Met Met Ala Tyr Leu Val Val Ser
 225 230 235 240

10 Gly Leu Phe Leu Thr Arg Leu Arg Arg Pro Ile Gly Lys Met Thr Ile
 245 250 255

15 Thr Glu Gln Lys Tyr Glu Gly Glu Tyr Arg Tyr Val Asn Ser Arg Leu
 260 265 270

20 Ile Thr Asn Ser Glu Glu Ile Ala Phe Tyr Asn Gly Asn Lys Arg Glu
 275 280 285

25 Lys Gln Thr Val His Ser Val Phe Arg Lys Leu Val Glu His Leu His
 290 295 300

30 Asn Phe Ile Leu Phe Arg Phe Ser Met Gly Phe Ile Asp Ser Ile Ile
 305 310 315 320

35 Ala Lys Tyr Leu Ala Thr Val Val Gly Tyr Leu Val Val Ser Arg Pro
 325 330 335

40 Phe Leu Asp Leu Ser His Pro Arg His Leu Lys Ser Thr His Ser Glu
 340 345 350

45 Leu Leu Glu Asp Tyr Tyr Gln Ser Gly Arg Met Leu Leu Arg Met Ser
 355 360 365

50 Gln Ala Leu Gly Arg Ile Val Leu Ala Gly Arg Glu Met Thr Arg Leu
 370 375 380

55 Ala Gly Phe Thr Ala Arg Ile Thr Glu Leu Met Gln Val Leu Lys Asp
 385 390 395 400

Leu Asn His Gly Lys Tyr Glu Arg Thr Met Val Ser Gln Gln Glu Lys
 405 410 415

Gly Ile Glu Gly Val Gln Val Ile Pro Leu Ile Pro Gly Ala Gly Glu
 420 425 430

Ile Ile Ile Ala Asp Asn Ile Ile Lys Phe Asp His Val Pro Leu Ala
 435 440 445

Thr Pro Asn Gly Asp Val Leu Ile Arg Asp Leu Asn Phe Glu Val Arg
 450 455 460

EP 1 217 066 A1

Ser Gly Ala Asn Val Leu Ile Cys Gly Pro Asn Gly Cys Gly Lys Ser
465 470 475 480

5 Ser Leu Phe Arg Val Leu Gly Glu Leu Trp Pro Leu Phe Gly Gly Arg
485 490 495

Leu Thr Lys Pro Glu Arg Gly Lys Leu Phe Tyr Val Pro Gln Arg Pro
10 500 505 510

Tyr Met Thr Leu Gly Thr Leu Arg Asp Gln Val Ile Tyr Pro Asp Gly
515 520 525

15 Arg Glu Asp Gln Lys Arg Lys Gly Ile Ser Asp Leu Val Leu Lys Glu
530 535 540

Tyr Leu Asp Asn Val Gln Leu Gly His Ile Leu Glu Arg Glu Gly Gly
20 545 550 555 560

Trp Asp Ser Val Gln Asp Trp Met Asp Val Leu Ser Gly Gly Glu Lys
565 570 575

25 Gln Arg Met Ala Met Ala Arg Leu Phe Tyr His Lys Pro Gln Phe Ala
580 585 590

Ile Leu Asp Glu Cys Thr Ser Ala Val Ser Val Asp Val Glu Gly Tyr
30 595 600 605

Ile Tyr Ser His Cys Arg Lys Val Gly Ile Thr Leu Phe Thr Val Ser
610 615 620

35 His Arg Lys Ser Leu Trp Lys His His Glu Tyr Tyr Leu His Met Asp
625 630 635 640

Gly Arg Gly Asn Tyr Glu Phe Lys Gln Ile Thr Glu Asp Thr Val Glu
40 645 650 655

Phe Gly Ser

45

<210> 73

50 <211> 606

<212> PRT

<213> Homo sapiens

55 <400> 73

Met Ala Val Ala Gly Pro Ala Pro Gly Ala Gly Ala Arg Pro Arg Leu

EP 1 217 066 A1

	1	5	10	15
5	Asp Leu Gln Phe Leu Gln Arg Phe Leu Gln Ile Leu Lys Val Leu Phe			
	20	25		30
10	Pro Ser Trp Ser Ser Gln Asn Ala Leu Met Phe Leu Thr Leu Leu Cys			
	35	40		45
	Leu Thr Leu Leu Glu Gln Phe Val Ile Tyr Gln Val Gly Leu Ile Pro			
	50	55	60	
15	Ser Gln Tyr Tyr Gly Val Leu Gly Asn Lys Asp Leu Glu Gly Phe Lys			
	65	70	75	80
20	Thr Leu Thr Phe Leu Ala Val Met Leu Ile Val Leu Asn Ser Thr Leu			
	85	90		95
	Lys Ser Phe Asp Gln Phe Thr Cys Asn Leu Leu Tyr Val Ser Trp Arg			
	100	105		110
25	Lys Asp Leu Thr Glu His Leu His Arg Leu Tyr Phe Arg Gly Arg Ala			
	115	120	125	
30	Tyr Tyr Thr Leu Asn Val Leu Arg Asp Asp Ile Asp Asn Pro Asp Gln			
	130	135	140	
	Arg Ile Ser Gln Asp Val Glu Arg Phe Cys Arg Gln Leu Ser Ser Met			
	145	150	155	160
35	Ala Ser Lys Leu Ile Ile Ser Pro Phe Thr Leu Val Tyr Tyr Thr Tyr			
	165	170		175
40	Gln Cys Phe Gln Ser Thr Gly Trp Leu Gly Pro Val Ser Ile Phe Gly			
	180	185	190	
	Tyr Phe Ile Leu Gly Thr Val Val Asn Lys Thr Leu Met Gly Pro Ile			
	195	200	205	
45	Val Met Lys Leu Val His Gln Glu Lys Leu Glu Gly Asp Phe Arg Phe			
	210	215	220	
50	Lys His Met Gln Ile Arg Val Asn Ala Glu Pro Ala Ala Phe Tyr Arg			
	225	230	235	240
	Ala Gly His Val Glu His Met Arg Thr Asp Arg Arg Leu Gln Arg Leu			
	245	250		255
55	Leu Gln Thr Gln Arg Glu Leu Met Ser Lys Glu Leu Trp Leu Tyr Ile			

EP 1 217 066 A1

	260	265	270
5	Gly Ile Asn Thr Phe Asp Tyr Leu Gly Ser Ile Leu Ser Tyr Val Val 275	280	285
10	Ile Ala Ile Pro Ile Phe Ser Gly Val Tyr Gly Asp Leu Ser Pro Ala 290	295	300
15	Glu Leu Ser Thr Leu Val Ser Lys Asn Ala Phe Val Cys Ile Tyr Leu 305	310	315
20	Ile Ser Cys Phe Thr Gln Leu Ile Asp Leu Ser Thr Thr Leu Ser Asp 325	330	335
25	Val Ala Gly Tyr Thr His Arg Ile Gly Gln Leu Arg Glu Thr Leu Leu 340	345	350
30	Asp Met Ser Leu Lys Ser Gln Asp Cys Glu Ile Leu Gly Glu Ser Glu 355	360	365
35	Trp Gly Leu Asp Thr Pro Pro Gly Trp Pro Ala Ala Glu Pro Ala Asp 370	375	380
40	Thr Ala Phe Leu Leu Glu Arg Val Ser Ile Ser Ala Pro Ser Ser Asp 385	390	395
45	Lys Pro Leu Ile Lys Asp Leu Ser Leu Lys Ile Ser Glu Gly Gln Ser 405	410	415
50	Leu Leu Ile Thr Gly Asn Thr Gly Thr Gly Lys Thr Ser Leu Leu Arg 420	425	430
55	Val Leu Gly Gly Leu Trp Thr Ser Thr Arg Gly Ser Val Gln Met Leu 435	440	445
	Thr Asp Phe Gly Pro His Gly Val Leu Phe Leu Pro Gln Lys Pro Phe 450	455	460
	Phe Thr Asp Gly Thr Leu Arg Glu Gln Val Ile Tyr Pro Leu Lys Glu 465	470	475
	Val Tyr Pro Asp Ser Gly Ser Ala Asp Asp Glu Arg Ile Leu Arg Phe 485	490	495
	Leu Glu Leu Ala Gly Leu Ser Asn Leu Val Ala Arg Thr Glu Gly Leu 500	505	510
	Asp Gln Gln Val Asp Trp Asn Trp Tyr Asp Val Leu Ser Pro Gly Glu		

EP 1 217 066 A1

	515	520	525
5	Met Gln Arg Leu Ser Phe Ala Arg Leu Phe Tyr Leu Gln Pro Lys Tyr		
	530	535	540
	Ala Val Leu Asp Glu Ala Thr Ser Ala Leu Thr Glu Glu Val Glu Ser		
10	545	550	555
	Glu Leu Tyr Arg Ile Gly Gln Gln Leu Gly Met Thr Phe Ile Ser Val		
	565	570	575
15	Gly His Arg Gln Ser Leu Glu Lys Phe His Ser Leu Val Leu Lys Leu		
	580	585	590
20	Cys Gly Gly Gly Arg Trp Glu Leu Met Arg Ile Lys Val Glu		
	595	600	605
25	<210> 74		
	<211> 599		
	<212> PRT		
	<213> Homo sapiens		
30	<400> 74		
	Met Ala Asp Lys Leu Thr Arg Ile Ala Ile Val Asn His Asp Lys Cys		
	1	5	10
	Lys Pro Lys Lys Cys Arg Gln Glu Cys Lys Ser Cys Pro Val Val		
35	20	25	30
	Arg Met Gly Lys Leu Cys Ile Glu Val Thr Pro Gln Ser Lys Ile Ala		
	35	40	45
40	Trp Ile Ser Glu Thr Leu Cys Ile Gly Cys Gly Ile Cys Ile Lys Lys		
	50	55	60
45	Cys Pro Phe Gly Ala Leu Ser Ile Val Asn Leu Pro Ser Asn Leu Glu		
	65	70	75
	Lys Glu Thr Thr His Arg Tyr Cys Ala Asn Ala Phe Lys Leu His Arg		
	85	90	95
50	Leu Pro Ile Pro Arg Pro Gly Glu Val Leu Gly Leu Val Gly Thr Asn		
	100	105	110
55	Gly Ile Gly Lys Ser Ala Ala Leu Lys Ile Leu Ala Gly Lys Gln Lys		
	115	120	125

Pro Asn Leu Gly Lys Tyr Asp Asp Pro Pro Asp Trp Gln Glu Ile Leu
 5 130 135 140

Thr Tyr Phe Arg Gly Ser Glu Leu Gln Asn Tyr Phe Thr Lys Ile Leu
 145 150 155 160

10 Glu Asp Asp Leu Lys Ala Ile Ile Lys Pro Gln Tyr Val Ala Arg Phe
 165 170 175

15 Leu Arg Leu Ala Lys Gly Thr Val Gly Ser Ile Leu Asp Arg Lys Asp
 180 185 190

20 Glu Thr Lys Thr Gln Ala Ile Val Cys Gln Gln Leu Asp Leu Thr His
 195 200 205

25 Leu Lys Glu Arg Asn Val Glu Asp Leu Ser Gly Gly Glu Leu Gln Arg
 210 215 220

Phe Ala Cys Ala Val Val Cys Ile Gln Lys Ala Asp Ile Phe Met Phe
 225 230 235 240

Asp Glu Pro Ser Ser Tyr Leu Asp Val Lys Gln Arg Leu Lys Ala Ala
 245 250 255

30 Ile Thr Ile Arg Ser Leu Ile Asn Pro Asp Arg Tyr Ile Ile Val Val
 260 265 270

35 Glu His Asp Leu Ser Val Leu Asp Tyr Leu Ser Asp Phe Ile Cys Cys
 275 280 285

Leu Tyr Gly Val Pro Ser Ala Tyr Gly Val Val Thr Met Pro Phe Ser
 290 295 300

40 Val Arg Glu Gly Ile Asn Ile Phe Leu Asp Gly Tyr Val Pro Thr Glu
 305 310 315 320

45 Asn Leu Arg Phe Arg Asp Ala Ser Leu Val Phe Lys Val Ala Glu Thr
 325 330 335

Ala Asn Glu Glu Glu Val Lys Lys Met Cys Met Tyr Lys Tyr Pro Gly
 340 345 350

50 Met Lys Lys Lys Met Gly Glu Phe Glu Leu Ala Ile Val Ala Gly Glu
 355 360 365

55 Phe Thr Asp Ser Glu Ile Met Val Met Leu Gly Glu Asn Gly Thr Gly
 370 375 380

EP 1 217 066 A1

Lys Thr Thr Phe Ile Arg Met Leu Ala Gly Arg Leu Lys Pro Asp Glu
385 390 395 400
5

Gly Gly Glu Val Pro Val Leu Asn Val Ser Tyr Lys Pro Gln Lys Ile
405 410 415

Ser Pro Lys Ser Thr Gly Ser Val Arg Gln Leu Leu His Glu Lys Ile
420 425 430
10

Arg Asp Ala Tyr Thr His Pro Gln Phe Val Thr Asp Val Met Lys Pro
435 440 445
15

Leu Gln Ile Glu Asn Ile Ile Asp Gln Glu Val Gln Thr Leu Ser Gly
450 455 460

Gly Glu Leu Gln Arg Val Arg Leu Arg Leu Cys Leu Gly Lys Pro Ala
465 470 475 480
20

Asp Val Tyr Leu Ile Asp Glu Pro Ser Ala Tyr Leu Asp Ser Glu Gln
485 490 495
25

Arg Leu Met Ala Ala Arg Val Val Lys Arg Phe Ile Leu His Ala Lys
500 505 510

Lys Thr Ala Phe Val Val Glu His Asp Phe Ile Met Ala Thr Tyr Leu
515 520 525
30

Ala Asp Arg Val Ile Val Phe Asp Gly Val Pro Ser Lys Asn Thr Val
530 535 540
35

Ala Asn Ser Pro Gln Thr Leu Leu Ala Gly Met Asn Lys Phe Leu Ser
545 550 555 560

Gln Leu Glu Ile Thr Phe Arg Arg Asp Pro Asn Asn Tyr Arg Pro Arg
565 570 575
40

Ile Asn Lys Leu Asn Ser Ile Lys Asp Val Glu Gln Lys Lys Ser Gly
580 585 590
45

Asn Tyr Phe Phe Leu Asp Asp
595

50

<210> 75
55 <211> 807
<212> PRT

<213> Homo sapiens

5 <400> 75
Met Pro Lys Ala Pro Lys Gln Gln Pro Pro Glu Pro Glu Trp Ile Gly
1 5 10 15

10 Asp Gly Glu Ser Thr Ser Pro Ser Asp Lys Val Val Lys Lys Gly Lys
20 25 30

15 Lys Asp Lys Lys Ile Lys Lys Thr Phe Phe Glu Glu Leu Ala Val Glu
35 40 45

20 Asp Lys Gln Ala Gly Glu Glu Lys Val Leu Lys Glu Lys Glu Gln
50 55 60

25 Gln Gln Gln Gln Gln Gln Lys Lys Lys Arg Asp Thr Arg
65 70 75 80

30 Lys Gly Arg Arg Lys Lys Asp Val Asp Asp Gly Glu Glu Lys Glu
85 90 95

35 Leu Met Glu Arg Leu Lys Leu Ser Val Pro Thr Ser Asp Glu Glu
100 105 110

40 Asp Glu Val Pro Ala Pro Lys Pro Arg Gly Gly Lys Lys Thr Lys Gly
115 120 125

45 Gly Asn Val Phe Ala Ala Leu Ile Gln Asp Gln Ser Glu Glu Glu
130 135 140

50 Glu Glu Glu Lys His Pro Pro Lys Pro Ala Lys Pro Glu Lys Asn Arg
145 150 155 160

55 Ile Asn Lys Ala Val Ser Glu Glu Gln Gln Pro Ala Leu Lys Gly Lys
165 170 175

60 Lys Gly Lys Glu Glu Lys Ser Lys Gly Lys Ala Lys Pro Gln Asn Lys
180 185 190

65 Phe Ala Ala Leu Asp Asn Glu Glu Asp Lys Glu Glu Glu Ile Ile
195 200 205

70 Lys Glu Lys Glu Pro Pro Lys Gln Gly Lys Glu Lys Ala Lys Lys Ala
210 215 220

75 Glu Gln Met Glu Tyr Glu Arg Gln Val Ala Ser Leu Lys Ala Ala Asn
225 230 235 240

EP 1 217 066 A1

Ala Ala Glu Asn Asp Phe Ser Val Ser Gln Ala Glu Met Ser Ser Arg
 245 250 255

5 Gln Ala Met Leu Glu Asn Ala Ser Asp Ile Lys Leu Glu Lys Phe Ser
 260 265 270

10 Ile Ser Ala His Gly Lys Glu Leu Phe Val Asn Ala Asp Leu Tyr Ile
 275 280 285

15 Val Ala Gly Arg Arg Tyr Gly Leu Val Gly Pro Asn Gly Lys Gly Lys
 290 295 300

20 Thr Thr Leu Leu Lys His Ile Ala Asn Arg Ala Leu Ser Ile Pro Pro
 305 310 315 320

25 Asn Ile Asp Val Leu Leu Cys Glu Gln Glu Val Val Ala Asp Glu Thr
 325 330 335

30 Pro Ala Val Gln Ala Val Leu Arg Ala Asp Thr Lys Arg Leu Lys Leu
 340 345 350

35 Leu Glu Glu Glu Arg Arg Leu Gln Gly Gln Leu Glu Gln Gly Asp Asp
 355 360 365

40 Thr Ala Ala Glu Arg Leu Glu Lys Val Tyr Glu Glu Leu Arg Ala Thr
 370 375 380

45 Gly Ala Ala Ala Ala Glu Ala Lys Ala Arg Arg Ile Leu Ala Gly Leu
 385 390 395 400

50 Gly Phe Asp Pro Glu Met Gln Asn Arg Pro Thr Gln Lys Phe Ser Gly
 405 410 415

55 Gly Trp Arg Met Arg Val Ser Leu Ala Arg Ala Leu Phe Met Glu Pro
 420 425 430

60 Thr Leu Leu Met Leu Asp Glu Pro Thr Asn His Leu Asp Leu Asn Ala
 435 440 445

65 Val Ile Trp Leu Asn Asn Tyr Leu Gln Gly Trp Arg Lys Thr Leu Leu
 450 455 460

70 Ile Val Ser His Asp Gln Gly Phe Leu Asp Asp Val Cys Thr Asp Ile
 465 470 475 480

75 Ile His Leu Asp Ala Gln Arg Leu His Tyr Tyr Arg Gly Asn Tyr Met
 485 490 495

EP 1 217 066 A1

Thr Phe Lys Lys Met Tyr Gln Gln Lys Glu Leu Leu Lys Gln
 500 505 510

5 Tyr Glu Lys Gln Glu Lys Lys Leu Lys Glu Leu Lys Ala Gly Gly Lys
 515 520 525

10 Ser Thr Lys Gln Ala Glu Lys Gln Thr Lys Glu Ala Leu Thr Arg Lys
 530 535 540

15 Gln Gln Lys Cys Arg Arg Lys Asn Gln Asp Glu Glu Ser Gln Glu Ala
 545 550 555 560

20 Pro Glu Leu Leu Lys Arg Pro Lys Glu Tyr Thr Val Arg Phe Thr Phe
 565 570 575

25 Pro Asp Pro Pro Pro Leu Ser Pro Pro Val Leu Gly Leu His Gly Val
 580 585 590

30 Thr Phe Gly Tyr Gln Gly Gln Lys Pro Leu Phe Lys Asn Leu Asp Phe
 595 600 605

35 Gly Ile Asp Met Asp Ser Arg Ile Cys Ile Val Gly Pro Asn Gly Val
 610 615 620

40 Gly Lys Ser Thr Leu Leu Leu Leu Thr Gly Lys Leu Thr Pro Thr
 625 630 635 640

His Gly Glu Met Arg Lys Asn His Arg Leu Lys Ile Gly Phe Phe Asn
 645 650 655

45 Gln Gln Tyr Ala Glu Gln Leu Arg Met Glu Glu Thr Pro Thr Glu Tyr
 660 665 670

50 Leu Gln Arg Gly Phe Asn Leu Pro Tyr Gln Asp Ala Arg Lys Cys Leu
 675 680 685

55 Gly Arg Phe Gly Leu Glu Ser His Ala His Thr Ile Gln Ile Cys Lys
 690 695 700

Leu Ser Gly Gly Gln Lys Ala Arg Val Val Phe Ala Glu Leu Ala Cys
 705 710 715 720

Arg Glu Pro Asp Val Leu Ile Leu Asp Glu Pro Thr Asn Asn Leu Asp
 725 730 735

Ile Glu Ser Ile Asp Ala Leu Gly Glu Ala Ile Asn Glu Tyr Lys Gly
 740 745 750

EP 1 217 066 A1

Ala Val Ile Val Val Ser His Asp Ala Arg Leu Ile Thr Glu Thr Asn
755 760 765

5

Cys Gln Leu Trp Val Val Glu Glu Gln Ser Val Ser Gln Ile Asp Gly
770 775 780

10

Asp Phe Glu Asp Tyr Lys Arg Glu Val Leu Glu Ala Leu Gly Glu Val
785 790 795 800

Met Val Ser Arg Pro Arg Glu
805

15

<210> 76

20

<211> 634

<212> PRT

<213> Homo sapiens

<400> 76

25

Met Pro Ser Asp Leu Ala Lys Lys Lys Ala Ala Lys Lys Lys Glu Ala
1 5 10 15

30

Ala Lys Ala Arg Gln Arg Pro Arg Lys Gly His Glu Glu Asn Gly Asp
20 25 30

Val Val Thr Glu Pro Gln Val Ala Glu Lys Asn Glu Ala Asn Gly Arg
35 40 45

35

Glu Thr Thr Glu Val Asp Leu Leu Thr Lys Glu Leu Glu Asp Phe Glu
50 55 60

40

Met Lys Lys Ala Ala Ala Arg Ala Val Thr Gly Val Leu Ala Ser His
65 70 75 80

Pro Asn Ser Thr Asp Val His Ile Ile Asn Leu Ser Leu Thr Phe His
85 90 95

45

Gly Gln Glu Leu Leu Ser Asp Thr Lys Leu Glu Leu Asn Ser Gly Arg
100 105 110

50

Arg Tyr Gly Leu Ile Gly Leu Asn Gly Ile Gly Lys Ser Met Leu Leu
115 120 125

Ser Ala Ile Gly Lys Arg Glu Val Pro Ile Pro Glu His Ile Asp Ile
130 135 140

55

Tyr His Leu Thr Arg Glu Met Pro Pro Ser Asp Lys Thr Pro Leu His

EP 1 217 066 A1

	145	150	155	160
5	Cys Val Met Glu Val Asp Thr Glu Arg Ala Met Leu Glu Lys Glu Ala			
	165	170	175	
	Glu Arg Leu Ala His Glu Asp Ala Glu Cys Glu Lys Leu Met Glu Leu			
10	180	185	190	
	Tyr Glu Arg Leu Glu Glu Leu Asp Ala Asp Lys Ala Glu Met Arg Ala			
	195	200	205	
15	Ser Arg Ile Leu His Gly Leu Gly Phe Thr Pro Ala Met Gln Arg Lys			
	210	215	220	
	Lys Leu Lys Asp Phe Ser Gly Gly Trp Arg Met Arg Val Ala Leu Ala			
20	225	230	235	240
	Arg Ala Leu Phe Ile Arg Pro Phe Met Leu Leu Leu Asp Glu Pro Thr			
	245	250	255	
25	Asn His Leu Asp Leu Asp Ala Cys Val Trp Leu Glu Glu Leu Lys			
	260	265	270	
	Thr Phe Lys Arg Ile Leu Val Leu Val Ser His Ser Gln Asp Phe Leu			
30	275	280	285	
	Asn Gly Val Cys Thr Asn Ile Ile His Met His Asn Lys Lys Leu Lys			
	290	295	300	
35	Tyr Tyr Thr Gly Asn Tyr Asp Gln Tyr Val Lys Thr Arg Leu Glu Leu			
	305	310	315	320
	Glu Glu Asn Gln Met Lys Arg Phe His Trp Glu Gln Asp Gln Ile Ala			
40	325	330	335	
	His Met Lys Asn Tyr Ile Ala Arg Phe Gly His Gly Ser Ala Lys Leu			
	340	345	350	
45	Ala Arg Gln Ala Gln Ser Lys Glu Lys Thr Leu Gln Lys Met Met Ala			
	355	360	365	
	Ser Gly Leu Thr Glu Arg Val Val Ser Asp Lys Thr Leu Ser Phe Tyr			
50	370	375	380	
	Phe Pro Pro Cys Gly Lys Ile Pro Pro Pro Val Ile Met Val Gln Asn			
	385	390	395	400
55	Val Ser Phe Lys Tyr Thr Lys Asp Gly Pro Cys Ile Tyr Asn Asn Leu			

EP 1 217 066 A1

	405	410	415
5	Glu Phe Gly Ile Asp Leu Asp Thr Arg Val Ala Leu Val Gly Pro Asn 420	425	430
	Gly Ala Gly Lys Ser Thr Leu Leu Lys Leu Leu Thr Gly Glu Leu Leu 435	440	445
10	Pro Thr Asp Gly Met Ile Arg Lys His Ser His Val Lys Ile Gly Arg 450	455	460
	Tyr His Gln His Leu Gln Glu Gln Leu Asp Leu Asp Leu Ser Pro Leu 465	470	480
	Glu Tyr Met Met Lys Cys Tyr Pro Glu Ile Lys Glu Lys Glu Glu Met 485	490	495
20	Arg Lys Ile Ile Gly Arg Tyr Gly Leu Thr Gly Lys Gln Gln Val Ser 500	505	510
	Pro Ile Arg Asn Leu Ser Asp Gly Gln Lys Cys Arg Val Cys Leu Ala 515	520	525
	Trp Leu Ala Trp Gln Asn Pro His Met Leu Phe Leu Asp Glu Pro Thr 530	535	540
30	Asn His Leu Asp Ile Glu Thr Ile Asp Ala Leu Ala Asp Ala Ile Asn 545	550	555
	Glu Phe Glu Gly Gly Met Met Leu Val Ser His Asp Phe Arg Leu Ile 565	570	575
	Gln Gln Val Ala Gln Glu Ile Trp Val Cys Glu Lys Gln Thr Ile Thr 580	585	590
40	Lys Trp Pro Gly Asp Ile Leu Ala Tyr Lys Glu His Leu Lys Ser Lys 595	600	605
	Leu Val Asp Glu Glu Pro Gln Leu Thr Lys Arg Thr His Asn Val Cys 610	615	620
	Thr Leu Thr Leu Ala Ser Leu Pro Arg Pro 625	630	
55	<210> 77		
	<211> 709		

<212> PRT
 <213> Homo sapiens

5 <400> 77
 Met Ala Thr Cys Ala Glu Ile Leu Arg Ser Glu Phe Pro Glu Ile Asp
 1 5 10 15
 10 Gly Gln Val Phe Asp Tyr Val Thr Gly Val Leu His Ser Gly Ser Ala
 20 25 30
 15 Asp Phe Glu Ser Val Asp Asp Leu Val Glu Ala Val Gly Glu Leu Leu
 35 40 45
 20 Gln Glu Val Ser Gly Asp Ser Lys Asp Asp Ala Gly Ile Arg Ala Val
 50 55 60
 25 Cys Gln Arg Met Tyr Asn Thr Leu Arg Leu Ala Glu Pro Gln Ser Gln
 65 70 75 80
 30 Gly Asn Ser Gln Val Leu Leu Asp Ala Pro Ile Gln Leu Ser Lys Ile
 85 90 95
 35 Thr Glu Asn Tyr Asp Cys Gly Thr Lys Leu Pro Gly Leu Leu Lys Arg
 100 105 110
 40 Glu Gln Ser Ser Thr Val Asn Ala Lys Lys Leu Glu Lys Ala Glu Ala
 115 120 125
 45 Arg Leu Lys Ala Lys Gln Glu Lys Arg Ser Glu Lys Asp Thr Leu Lys
 130 135 140
 50 Thr Ser Asn Pro Leu Val Leu Glu Ala Ser Ala Ser Gln Ala Gly
 145 150 155 160
 55 Ser Arg Lys Glu Ser Arg Leu Glu Ser Ser Gly Lys Asn Lys Ser Tyr
 165 170 175
 60 Asp Val Arg Ile Glu Asn Phe Asp Val Ser Phe Gly Asp Arg Val Leu
 180 185 190
 65 Leu Ala Gly Ala Asp Val Asn Leu Ala Trp Gly Arg Arg Tyr Gly Leu
 195 200 205
 70 Val Gly Arg Asn Gly Leu Gly Lys Thr Thr Leu Leu Lys Met Leu Ala
 210 215 220
 75 Thr Arg Ser Leu Arg Val Pro Ala His Ile Ser Leu Leu His Val Glu
 225 230 235 240

Gln Glu Val Ala Gly Asp Asp Thr Pro Ala Leu Gln Ser Val Leu Glu
 5 245 250 255

Ser Asp Ser Val Arg Glu Asp Leu Leu Arg Arg Glu Arg Glu Leu Thr
 10 260 265 270

Ala Gln Ile Ala Ala Gly Arg Ala Glu Gly Ser Glu Ala Ala Glu Leu
 15 275 280 285

Ala Glu Ile Tyr Ala Lys Leu Glu Glu Ile Glu Ala Asp Lys Ala Pro
 20 290 295 300

Ala Arg Ala Ser Val Ile Leu Ala Gly Leu Gly Phe Thr Pro Lys Met
 25 305 310 315 320

Gln Gln Gln Pro Thr Arg Glu Phe Ser Gly Gly Trp Arg Met Arg Leu
 30 325 330 335

Ala Leu Ala Arg Ala Leu Phe Ala Arg Pro Asp Leu Leu Leu Asp
 35 340 345 350

Glu Pro Thr Asn Met Leu Asp Val Arg Ala Ile Leu Trp Leu Glu Asn
 40 355 360 365

Tyr Leu Gln Thr Trp Pro Ser Thr Ile Leu Val Val Ser His Asp Arg
 45 370 375 380

Asn Phe Leu Asn Ala Ile Ala Thr Asp Ile Ile His Leu His Ser Gln
 50 385 390 395 400

Arg Leu Asp Gly Tyr Arg Gly Asp Phe Glu Thr Phe Ile Lys Ser Lys
 55 405 410 415

Gln Glu Arg Leu Leu Asn Gln Gln Arg Glu Tyr Glu Ala Gln Gln Gln
 60 420 425 430

Tyr Arg Gln His Ile Gln Val Phe Ile Asp Arg Phe Arg Tyr Asn Ala
 65 435 440 445

Asn Arg Ala Ser Gln Val Gln Ser Lys Leu Lys Met Leu Glu Lys Leu
 70 450 455 460

Pro Glu Leu Arg Pro Val Asp Lys Glu Ser Glu Val Val Met Lys Phe
 75 465 470 475 480

Pro Asp Gly Phe Glu Lys Phe Ser Pro Pro Ile Leu Gln Leu Asp Glu
 80 485 490 495

	Val Asp Phe Tyr Tyr Asp Pro Lys His Val Ile Phe Ser Arg Leu Ser		
5	500	505	510
	Val Ser Ala Asp Leu Glu Ser Arg Ile Cys Val Val Gly Glu Asn Gly		
	515	520	525
10	Ala Gly Lys Ser Thr Met Leu Lys Leu Leu Leu Gly Asp Leu Ala Pro		
	530	535	540
15	Val Arg Gly Ile Arg His Ala His Arg Asn Leu Lys Ile Gly Tyr Phe		
	545	550	555
	Ser Gln His His Val Glu Gln Leu Asp Leu Asn Val Ser Ala Val Glu		
	565	570	575
20	Leu Leu Ala Arg Lys Phe Pro Gly Arg Pro Glu Glu Glu Tyr Arg His		
	580	585	590
25	Gln Leu Gly Arg Tyr Gly Ile Ser Gly Glu Leu Ala Met Arg Pro Leu		
	595	600	605
	Ala Ser Leu Ser Gly Gly Gln Lys Ser Arg Val Ala Phe Ala Gln Met		
	610	615	620
30	Thr Met Pro Cys Pro Asn Phe Tyr Ile Leu Asp Glu Pro Thr Asn His		
	625	630	635
	640		
35	Leu Asp Met Glu Thr Ile Glu Ala Leu Gly Arg Ala Leu Asn Asn Phe		
	645	650	655
	Arg Gly Gly Val Ile Leu Val Ser His Asp Glu Arg Phe Ile Arg Leu		
	660	665	670
40	Val Cys Arg Glu Leu Trp Val Cys Glu Gly Gly Val Thr Arg Val		
	675	680	685
45	Glu Gly Gly Phe Asp Gln Tyr Arg Ala Leu Leu Gln Glu Gln Phe Arg		
	690	695	700
	Arg Glu Gly Phe Leu		
	705		
50	<210> 78		
	<211> 674		
55	<212> PRT		

<213> Homo sapiens

5 <400> 78
Met Ala Ala Phe Ser Val Gly Thr Ala Met Asn Ala Ser Ser Tyr Ser
 1 5 10 15

10 Ala Glu Met Thr Glu Pro Lys Ser Val Cys Val Ser Val Asp Glu Val
 20 25 30

15 Val Ser Ser Asn Met Glu Ala Thr Glu Thr Asp Leu Leu Asn Gly His
 35 40 45

20 Leu Lys Lys Val Asp Asn Asn Leu Thr Glu Ala Gln Arg Phe Ser Ser
 50 55 60

25 Leu Pro Arg Arg Ala Ala Val Asn Ile Glu Phe Arg Asp Leu Ser Tyr
 65 70 75 80

30 Ser Val Pro Glu Gly Pro Trp Trp Arg Lys Lys Gly Tyr Lys Thr Leu
 85 90 95

35 Leu Lys Gly Ile Ser Gly Lys Phe Asn Ser Gly Glu Leu Val Ala Ile
 100 105 110

40 Met Gly Pro Ser Gly Ala Gly Lys Ser Thr Leu Met Asn Ile Leu Ala
 115 120 125

45 Gly Tyr Arg Glu Thr Gly Met Lys Gly Ala Val Leu Ile Asn Gly Leu
 130 135 140

50 Pro Arg Asp Leu Arg Cys Phe Arg Lys Val Ser Cys Tyr Ile Met Gln
 145 150 155 160

55 Asp Asp Met Leu Leu Pro His Leu Thr Val Gln Glu Ala Met Met Val
 165 170 175

60 Ser Ala His Leu Lys Leu Gln Glu Lys Asp Glu Gly Arg Arg Glu Met
 180 185 190

65 Val Lys Glu Ile Leu Thr Ala Leu Gly Leu Leu Ser Cys Ala Asn Thr
 195 200 205

70 Arg Thr Gly Ser Leu Ser Gly Gly Gln Arg Lys Arg Leu Ala Ile Ala
 210 215 220

75 Leu Glu Leu Val Asn Asn Pro Pro Val Met Phe Phe Asp Glu Pro Thr
 225 230 235 240

Ser Gly Leu Asp Ser Ala Ser Cys Phe Gln Val Val Ser Leu Met Lys
 245 250 255
 5 Gly Leu Ala Gln Gly Gly Arg Ser Ile Ile Cys Thr Ile His Gln Pro
 260 265 270
 10 Ser Ala Lys Leu Phe Glu Leu Phe Asp Gln Leu Tyr Val Leu Ser Gln
 275 280 285
 Gly Gln Cys Val Tyr Arg Gly Lys Val Cys Asn Leu Val Pro Tyr Leu
 290 295 300
 15 Arg Asp Leu Gly Leu Asn Cys Pro Thr Tyr His Asn Pro Ala Asp Phe
 305 310 315 320
 20 Val Met Glu Val Ala Ser Gly Glu Tyr Gly Asp Gln Asn Ser Arg Leu
 325 330 335
 Val Arg Ala Val Arg Glu Gly Met Cys Asp Ser Asp His Lys Arg Asp
 340 345 350
 25 Leu Gly Gly Asp Ala Glu Val Asn Pro Phe Leu Trp His Arg Pro Ser
 355 360 365
 30 Glu Glu Val Lys Gln Thr Lys Arg Leu Lys Gly Leu Arg Lys Asp Ser
 370 375 380
 Ser Ser Met Glu Gly Cys His Ser Phe Ser Ala Ser Cys Leu Thr Gln
 385 390 395 400
 35 Phe Cys Ile Leu Phe Lys Arg Thr Phe Leu Ser Ile Met Arg Asp Ser
 405 410 415
 40 Val Leu Thr His Leu Arg Ile Thr Ser His Ile Gly Ile Gly Leu Leu
 420 425 430
 Ile Gly Leu Leu Tyr Leu Gly Ile Gly Asn Glu Thr Lys Lys Val Leu
 435 440 445
 45 Ser Asn Ser Gly Phe Leu Phe Phe Ser Met Leu Phe Leu Met Phe Ala
 450 455 460
 Ala Leu Met Pro Thr Val Leu Thr Phe Pro Leu Glu Met Gly Val Phe
 465 470 475 480
 Leu Arg Glu His Leu Asn Tyr Trp Tyr Ser Leu Lys Ala Tyr Tyr Leu
 485 490 495
 55

EP 1 217 066 A1

Ala Lys Thr Met Ala Asp Val Pro Phe Gln Ile Met Phe Pro Val Ala
500 505 510

5 Tyr Cys Ser Ile Val Tyr Trp Met Thr Ser Gln Pro Ser Asp Ala Val
515 520 525

10 Arg Phe Val Leu Phe Ala Ala Leu Gly Thr Met Thr Ser Leu Val Ala
530 535 540

Gln Ser Leu Gly Leu Leu Ile Gly Ala Ala Ser Thr Ser Leu Gln Val
545 550 555 560

15 Ala Thr Phe Val Gly Pro Val Thr Ala Ile Pro Val Leu Leu Phe Ser
565 570 575

20 Gly Phe Phe Val Ser Phe Asp Thr Ile Pro Thr Tyr Leu Gln Trp Met
580 585 590

Ser Tyr Ile Ser Tyr Val Arg Tyr Gly Phe Glu Gly Val Ile Leu Ser
595 600 605

25 Ile Tyr Gly Leu Asp Arg Glu Asp Leu His Cys Asp Ile Asp Glu Thr
610 615 620

30 Cys His Phe Gln Lys Ser Glu Ala Ile Leu Arg Glu Leu Asp Val Glu
625 630 635 640

Asn Ala Lys Leu Tyr Leu Asp Phe Ile Val Leu Gly Ile Phe Phe Ile
645 650 655

35 Ser Leu Arg Leu Ile Ala Tyr Leu Val Leu Arg Tyr Lys Ile Arg Ala
660 665 670

40 Glu Arg

45 <210> 79
<211> 655
<212> PRT
<213> Homo sapiens

50 <400> 79
Met Ser Ser Ser Asn Val Glu Val Phe Ile Pro Val Ser Gln Gly Asn
1 5 10 15

55 Thr Asn Gly Phe Pro Ala Thr Val Ser Asn Asp Leu Lys Ala Phe Thr

EP 1 217 066 A1

	20	25	30
5	Glu Gly Ala Val Leu Ser Phe His Asn Ile Cys Tyr Arg Val Lys Leu 35	40	45
10	Lys Ser Gly Phe Leu Pro Cys Arg Lys Pro Val Glu Lys Glu Ile Leu 50	55	60
15	Ser Asn Ile Asn Gly Ile Met Lys Pro Gly Leu Asn Ala Ile Leu Gly 65	70	75
20	Pro Thr Gly Gly Lys Ser Ser Leu Leu Asp Val Leu Ala Ala Arg 85	90	95
25	Lys Asp Pro Ser Gly Leu Ser Gly Asp Val Leu Ile Asn Gly Ala Pro 100	105	110
30	Arg Pro Ala Asn Phe Lys Cys Asn Ser Gly Tyr Val Val Gln Asp Asp 115	120	125
35	Val Val Met Gly Thr Leu Thr Val Arg Glu Asn Leu Gln Phe Ser Ala 130	135	140
40	Ala Leu Arg Leu Ala Thr Thr Met Thr Asn His Glu Lys Asn Glu Arg 145	150	155
45	Ile Asn Arg Val Ile Glu Glu Leu Gly Leu Asp Lys Val Ala Asp Ser 165	170	175
50	Lys Val Gly Thr Gln Phe Ile Arg Gly Val Ser Gly Gly Glu Arg Lys 180	185	190
55	Arg Thr Ser Ile Gly Met Glu Leu Ile Thr Asp Pro Ser Ile Leu Ser 195	200	205
	Leu Asp Glu Pro Thr Thr Gly Leu Asp Ser Ser Thr Ala Asn Ala Val 210	215	220
	Leu Leu Leu Leu Lys Arg Met Ser Lys Gln Gly Arg Thr Ile Ile Phe 225	230	235
	Ser Ile His Gln Pro Arg Tyr Ser Ile Phe Lys Leu Phe Asp Ser Leu 245	250	255
	Thr Leu Leu Ala Ser Gly Arg Leu Met Phe His Gly Pro Ala Gln Glu 260	265	270
	Ala Leu Gly Tyr Phe Glu Ser Ala Gly Tyr His Cys Glu Ala Tyr Asn		

	275	280	285
5	Asn Pro Ala Asp Phe Phe Leu Asp Ile Ile Asn Gly Asp Ser Thr Ala		
	290	295	300
10	Val Ala Leu Asn Arg Glu Glu Asp Phe Lys Ala Thr Glu Ile Ile Glu		
	305	310	315
	Pro Ser Lys Gln Asp Lys Pro Leu Ile Glu Lys Leu Ala Glu Ile Tyr		
	325	330	335
15	Val Asn Ser Ser Phe Tyr Lys Glu Thr Lys Ala Glu Leu His Gln Leu		
	340	345	350
20	Ser Gly Gly Glu Lys Lys Lys Ile Thr Val Phe Lys Glu Ile Ser		
	355	360	365
25	Tyr Thr Thr Ser Phe Cys His Gln Leu Arg Trp Val Ser Lys Arg Ser		
	370	375	380
30	Phe Lys Asn Leu Leu Gly Asn Pro Gln Ala Ser Ile Ala Gln Ile Ile		
	385	390	395
	Val Thr Val Val Leu Gly Leu Val Ile Gly Ala Ile Tyr Phe Gly Leu		
	405	410	415
35	Lys Asn Asp Ser Thr Gly Ile Gln Asn Arg Ala Gly Val Leu Phe Phe		
	420	425	430
40	Leu Thr Thr Asn Gln Cys Phe Ser Ser Val Ser Ala Val Glu Leu Phe		
	435	440	445
45	Val Val Glu Lys Lys Leu Phe Ile His Glu Tyr Ile Ser Gly Tyr Tyr		
	450	455	460
50	Arg Val Ser Ser Tyr Phe Leu Gly Lys Leu Leu Ser Asp Leu Leu Pro		
	465	470	475
	Met Arg Met Leu Pro Ser Ile Ile Phe Thr Cys Ile Val Tyr Phe Met		
	485	490	495
55	Leu Gly Leu Lys Pro Lys Ala Asp Ala Phe Phe Val Met Met Phe Thr		
	500	505	510
60	Leu Met Met Val Ala Tyr Ser Ala Ser Ser Met Ala Leu Ala Ile Ala		
	515	520	525
65	Ala Gly Gln Ser Val Val Ser Val Ala Thr Leu Leu Met Thr Ile Cys		

EP 1 217 066 A1

	530	535	540
5	Phe Val Phe Met Met Ile Phe Ser Gly Leu Leu Val Asn Leu Thr Thr		
	545	550	555
	Ile Ala Ser Trp Leu Ser Trp Leu Gln Tyr Phe Ser Ile Pro Arg Tyr		
10	565	570	575
	Gly Phe Thr Ala Leu Gln His Asn Glu Phe Leu Gly Gln Asn Phe Cys		
	580	585	590
15	Pro Gly Leu Asn Ala Thr Gly Asn Asn Pro Cys Asn Tyr Ala Thr Cys		
	595	600	605
	Thr Gly Glu Glu Tyr Leu Val Lys Gln Gly Ile Asp Leu Ser Pro Trp		
20	610	615	620
	Gly Leu Trp Lys Asn His Val Ala Leu Ala Cys Met Ile Val Ile Phe		
	625	630	635
	Leu Thr Ile Ala Tyr Leu Lys Leu Leu Phe Leu Lys Lys Tyr Ser		
25	645	650	655
30	<210> 80		
	<211> 649		
	<212> PRT		
	<213> Homo sapiens		
35	<400> 80		
	Met Gly Asp Leu Ser Ser Leu Thr Pro Gly Gly Ser Met Gly Leu Gln		
	1	5	10
			15
40	Val Asn Arg Gly Ser Gln Ser Ser Leu Glu Gly Ala Pro Ala Thr Ala		
	20	25	30
45	Pro Glu Pro His Ser Leu Gly Ile Leu His Ala Ser Tyr Ser Val Ser		
	35	40	45
	His Arg Val Arg Pro Trp Trp Asp Ile Thr Ser Cys Arg Gln Gln Trp		
	50	55	60
50	Thr Arg Gln Ile Leu Lys Asp Val Ser Leu Tyr Val Glu Ser Gly Gln		
	65	70	75
			80
55	Ile Met Cys Ile Leu Gly Ser Ser Gly Ser Gly Lys Thr Thr Leu Leu		
	85	90	95

Asp Ala Met Ser Gly Arg Leu Gly Arg Ala Gly Thr Phe Leu Gly Glu
 100 105 110
 5

Val Tyr Val Asn Gly Arg Ala Leu Arg Arg Glu Gln Phe Gln Asp Cys
 115 120 125

10 Phe Ser Tyr Val Leu Gln Ser Asp Thr Leu Leu Ser Ser Leu Thr Val
 130 135 140

15 Arg Glu Thr Leu His Tyr Thr Ala Leu Leu Ala Ile Arg Arg Gly Asn
 145 150 155 160

Pro Gly Ser Phe Gln Lys Lys Val Glu Ala Val Met Ala Glu Leu Ser
 165 170 175

20 Leu Ser His Val Ala Asp Arg Leu Ile Gly Asn Tyr Ser Leu Gly Gly
 180 185 190

25 Ile Ser Thr Gly Glu Arg Arg Arg Val Ser Ile Ala Ala Gln Leu Leu
 195 200 205

Gln Asp Pro Lys Val Met Leu Phe Pro Thr Thr Gly Leu Asp Cys Met
 210 215 220

30 Thr Ala Asn Gln Ile Val Val Leu Leu Val Glu Leu Ala Arg Arg Asn
 225 230 235 240

35 Arg Ile Val Val Leu Thr Ile His Gln Pro Arg Ser Glu Leu Phe Gln
 245 250 255

Leu Phe Asp Lys Ile Ala Ile Leu Ser Phe Gly Glu Leu Ile Phe Cys
 260 265 270

40 Gly Thr Pro Ala Glu Met Leu Asp Phe Phe Asn Asp Cys Gly Tyr Pro
 275 280 285

45 Cys Pro Glu His Ser Asn Pro Phe Asp Phe Tyr Met Asp Leu Thr Ser
 290 295 300

Val Asp Thr Gln Ser Lys Glu Arg Glu Ile Glu Thr Ser Lys Arg Val
 305 310 315 320

50 Gln Met Ile Glu Ser Ala Tyr Lys Lys Ser Ala Ile Cys His Lys Thr
 325 330 335

55 Leu Lys Asn Ile Glu Arg Met Lys His Leu Lys Thr Leu Pro Met Val
 340 345 350

	Pro Phe Lys Thr Lys Asp Ser Pro Gly Val Phe Ser Lys Leu Gly Val		
5	355	360	365
	Leu Leu Arg Arg Val Thr Arg Asn Leu Val Arg Asn Lys Leu Ala Val		
	370	375	380
10	Ile Thr Arg Leu Leu Gln Asn Leu Ile Met Gly Leu Phe Leu Leu Phe		
	385	390	395
	400		
15	Phe Val Leu Arg Val Arg Ser Asn Val Leu Lys Gly Ala Ile Gln Asp		
	405	410	415
	Arg Val Gly Leu Leu Tyr Gln Phe Val Gly Ala Thr Pro Tyr Thr Gly		
	420	425	430
20	Met Leu Asn Ala Val Asn Leu Phe Pro Val Leu Arg Ala Val Ser Asp		
	435	440	445
25	Gln Glu Ser Gln Asp Gly Leu Tyr Gln Lys Trp Gln Met Met Leu Ala		
	450	455	460
	Tyr Ala Leu His Val Leu Pro Phe Ser Val Val Ala Thr Met Ile Phe		
	465	470	475
	480		
30	Ser Ser Val Cys Tyr Trp Thr Leu Gly Leu His Pro Glu Val Ala Arg		
	485	490	495
35	Phe Gly Tyr Phe Ser Ala Ala Leu Leu Ala Pro His Leu Ile Gly Glu		
	500	505	510
	Phe Leu Thr Leu Val Leu Leu Gly Ile Val Gln Asn Pro Asn Ile Val		
	515	520	525
40	Asn Ser Val Val Ala Leu Leu Ser Ile Ala Gly Val Leu Val Gly Ser		
	530	535	540
45	Gly Phe Leu Arg Asn Ile Gln Glu Met Pro Ile Pro Phe Lys Ile Ile		
	545	550	555
	560		
	Ser Tyr Phe Thr Phe Gln Lys Tyr Cys Ser Glu Ile Leu Val Val Asn		
	565	570	575
50	Glu Phe Tyr Gly Leu Asn Phe Thr Cys Gly Ser Ser Asn Val Ser Val		
	580	585	590
55	Thr Thr Asn Pro Met Cys Ala Phe Thr Gln Gly Ile Gln Phe Ile Glu		
	595	600	605

5 Lys Thr Cys Pro Gly Ala Thr Ser Arg Phe Thr Met Asn Phe Leu Ile
 610 615 620

 10 Leu Tyr Ser Phe Ile Pro Ala Leu Val Ile Leu Gly Ile Val Val Phe
 625 630 635 640

 15 Lys Ile Arg Asp His Leu Ile Ser Arg
 645

 20 <210> 81
 <211> 673
 <212> PRT
 25 <213> Homo sapiens

 30 <400> 81
 Met Ala Gly Lys Ala Ala Glu Glu Arg Gly Leu Pro Lys Gly Ala Thr
 1 5 10 15

 35 Pro Gln Asp Thr Ser Gly Leu Gln Asp Arg Leu Phe Ser Ser Glu Ser
 20 25 30

 40 Asp Asn Ser Leu Tyr Phe Thr Tyr Ser Gly Gln Pro Asn Thr Leu Glu
 35 40 45

 45 Val Arg Asp Leu Asn Tyr Gln Val Asp Leu Ala Ser Gln Val Pro Trp
 50 55 60

 50 Phe Glu Gln Leu Ala Gln Phe Lys Met Pro Trp Thr Ser Pro Ser Cys
 65 70 75 80

 55 Gln Asn Ser Cys Glu Leu Gly Ile Gln Asn Leu Ser Phe Lys Val Arg
 85 90 95

 60 Ser Gly Gln Met Leu Ala Ile Ile Gly Ser Ser Gly Cys Gly Arg Ala
 100 105 110

 65 Ser Leu Leu Asp Val Ile Thr Gly Arg Gly His Gly Gly Lys Ile Lys
 115 120 125

 70 Ser Gly Gln Ile Trp Ile Asn Gly Gln Pro Ser Ser Pro Gln Leu Val
 130 135 140

 75 Arg Lys Cys Val Ala His Val Arg Gln His Asn Gln Leu Leu Pro Asn
 145 150 155 160

EP 1 217 066 A1

Leu Thr Val Arg Glu Thr Leu Ala Phe Ile Ala Gln Met Arg Leu Pro
165 170 175

5 Arg Thr Phe Ser Gln Ala Gln Arg Asp Lys Arg Val Glu Asp Val Ile
180 185 190

10 Ala Glu Leu Arg Leu Arg Gln Cys Ala Asp Thr Arg Val Gly Asn Met
195 200 205

15 Tyr Val Arg Gly Leu Ser Gly Gly Glu Arg Arg Arg Val Ser Ile Gly
210 215 220

20 Val Gln Leu Leu Trp Asn Pro Gly Ile Leu Ile Leu Asp Glu Pro Thr
225 230 235 240

25 Ser Gly Leu Asp Ser Phe Thr Ala His Asn Leu Val Lys Thr Leu Ser
245 250 255

30 Arg Leu Ala Lys Gly Asn Arg Leu Val Leu Ile Ser Leu His Gln Pro
260 265 270

35 Arg Ser Asp Ile Phe Arg Leu Phe Asp Leu Val Leu Leu Met Thr Ser
275 280 285

40 Gly Thr Pro Ile Tyr Leu Gly Ala Ala Gln His Met Val Gln Tyr Phe
290 295 300

45 Thr Ala Ile Gly Tyr Pro Cys Pro Arg Tyr Ser Asn Pro Ala Asp Phe
305 310 315 320

Tyr Val Asp Leu Thr Ser Ile Asp Arg Arg Ser Arg Glu Gln Glu Leu
325 330 335

50 Ala Thr Arg Glu Lys Ala Gln Ser Leu Ala Ala Leu Phe Leu Glu Lys
340 345 350

55 Val Arg Asp Leu Asp Asp Phe Leu Trp Lys Ala Glu Thr Lys Asp Leu
355 360 365

Asp Glu Asp Thr Cys Val Glu Ser Ser Val Thr Pro Leu Asp Thr Asn
370 375 380

55 Cys Leu Pro Ser Pro Thr Lys Met Pro Gly Ala Val Gln Gln Phe Thr
385 390 395 400

Thr Leu Ile Arg Arg Gln Ile Ser Asn Asp Phe Arg Asp Leu Pro Thr
405 410 415

EP 1 217 066 A1

Leu Leu Ile His Gly Ala Glu Ala Cys Leu Met Ser Met Thr Ile Gly
420 425 430

5 Phe Leu Tyr Phe Gly His Gly Ser Ile Gln Leu Ser Phe Met Asp Thr
435 440 445

10 Ala Ala Leu Leu Phe Met Ile Gly Ala Leu Ile Pro Phe Asn Val Ile
450 455 460

Leu Asp Val Ile Ser Lys Cys Tyr Ser Glu Arg Ala Met Leu Tyr Tyr
465 470 475 480

15 Glu Leu Glu Asp Gly Leu Tyr Thr Thr Gly Pro Tyr Phe Phe Ala Lys
485 490 495

20 Ile Leu Gly Glu Leu Pro Glu His Cys Ala Tyr Ile Ile Tyr Gly
500 505 510

Met Pro Thr Tyr Trp Leu Ala Asn Leu Arg Pro Gly Leu Gln Pro Phe
515 520 525

25 Leu Leu His Phe Leu Leu Val Trp Leu Val Val Phe Cys Cys Arg Ile
530 535 540

30 Met Ala Leu Ala Ala Ala Leu Leu Pro Thr Phe His Met Ala Ser
545 550 555 560

35 Phe Phe Ser Asn Ala Leu Tyr Asn Ser Phe Tyr Leu Ala Gly Gly Phe
565 570 575

40 Met Ile Asn Leu Ser Ser Leu Trp Thr Val Pro Ala Trp Ile Ser Lys
580 585 590

Val Ser Phe Leu Arg Trp Cys Phe Glu Gly Leu Met Lys Ile Gln Phe
595 600 605

45 Ser Arg Arg Thr Tyr Lys Met Pro Leu Gly Asn Leu Thr Ile Ala Val
610 615 620

Ser Gly Asp Lys Ile Leu Ser Val Met Glu Leu Asp Ser Tyr Pro Leu
625 630 635 640

50 Tyr Ala Ile Tyr Leu Ile Val Ile Gly Leu Ser Gly Gly Phe Met Val
645 650 655

Leu Tyr Tyr Val Ser Leu Arg Phe Ile Lys Gln Lys Pro Ser Gln Asp
55 660 665 670

Trp

5

<210> 82

<211> 590

<212> PRT

<213> Streptomyces lincolnensis

<400> 82

Met Glu Arg Gly Pro Gln Met Ala Asn Arg Ile Glu Gly Lys Ala Val

1

5

10

15

Asp Lys Thr Ser Ile Lys His Phe Val Lys Leu Ile Arg Ala Ala Lys

20

25

30

Pro Arg Tyr Leu Phe Phe Val Ile Gly Ile Val Ala Gly Ile Ile Gly

35

40

45

25

Thr Leu Ile Gln Leu Gln Val Pro Lys Met Val Gln Pro Leu Ile Asn

50

55

60

30

Ser Phe Gly His Gly Val Asn Gly Gly Lys Val Ala Leu Val Ile Ala

65

70

75

80

35

Leu Tyr Ile Gly Ser Ala Ala Val Ser Ala Ile Ala Ala Ile Val Leu

85

90

95

40

Gly Ile Phe Gly Glu Ser Val Val Lys Asn Leu Arg Thr Arg Val Trp

100

105

110

45

Asp Lys Met Ile His Leu Pro Val Lys Tyr Phe Asp Glu Val Lys Thr

115

120

125

50

Gly Glu Met Ser Ser Arg Leu Ala Asn Asp Thr Thr Gln Val Lys Asn

130

135

140

55

Leu Ile Ala Asn Ser Ile Pro Gln Ala Phe Thr Ser Ile Leu Leu Leu

145

150

155

160

50

Val Gly Ser Ile Ile Phe Met Leu Gln Met Gln Trp Arg Leu Thr Leu

165

170

175

55

Ala Met Ile Ile Ala Val Pro Ile Val Met Leu Ile Met Phe Pro Ile

180

185

190

Met Thr Phe Gly Gln Lys Ile Gly Trp Thr Arg Gln Asp Ser Leu Ala

EP 1 217 066 A1

	195	200	205
5	Asn Phe Gln Gly Ile Ala Ser Glu Ser Leu Ser Glu Ile Arg Leu Val		
	210	215	220
	Lys Ser Ser Asn Ala Glu Lys Gln Ala Ser Lys Lys Ala Glu Asn Asp		
10	225	230	235
	Val Asn Ala Leu Tyr Lys Ile Gly Val Lys Glu Ala Val Phe Asp Gly		
	245	250	255
15	Leu Met Ser Pro Val Met Met Leu Ser Met Met Leu Met Ile Phe Gly		
	260	265	270
	Leu Leu Ala Tyr Gly Ile Tyr Leu Ile Ser Thr Gly Val Met Ser Leu		
20	275	280	285
	Gly Thr Leu Leu Gly Met Met Met Tyr Leu Met Asn Leu Ile Gly Val		
	290	295	300
25	Val Pro Thr Val Ala Thr Phe Phe Thr Glu Leu Ala Lys Ala Ser Gly		
	305	310	315
	Ser Thr Gly Arg Leu Thr Glu Leu Leu Asp Glu Glu Gln Glu Val Leu		
30	325	330	335
	His Gln Gly Asp Ser Leu Asp Leu Glu Gly Lys Thr Leu Ser Ala His		
	340	345	350
35	His Val Asp Phe Ala Tyr Asp Asp Ser Glu Gln Ile Leu His Asp Ile		
	355	360	365
	Ser Phe Glu Ala Gln Pro Asn Ser Ile Ile Ala Phe Ala Gly Pro Ser		
40	370	375	380
	Gly Gly Gly Lys Ser Thr Ile Phe Ser Leu Leu Glu Arg Phe Tyr Gln		
	385	390	395
45	Pro Thr Ala Gly Glu Ile Thr Ile Gly Gly Gln Pro Ile Asp Ser Val		
	405	410	415
	Ser Leu Glu Asn Trp Arg Ser Gln Ile Gly Phe Val Ser Gln Asp Ser		
50	420	425	430
	Ala Ile Met Ala Gly Thr Ile Arg Glu Asn Leu Thr Tyr Gly Leu Glu		
	435	440	445
55	Gly Asn Phe Thr Asp Glu Asp Leu Trp Gln Val Leu Asp Leu Ala Phe		

EP 1 217 066 A1

	450	455	460
5	Ala Arg Ser Phe Val Glu Asn Met Pro Asp Gln Leu Asn Thr Glu Val		
	465	470	475
	Gly Glu Arg Gly Val Lys Ile Ser Gly Gly Gln Arg Gln Arg Leu Ala		
10	485	490	495
	Ile Ala Arg Ala Phe Leu Arg Asn Pro Lys Ile Leu Met Leu Asp Glu		
	500	505	510
15	Ala Thr Ala Ser Leu Asp Ser Glu Ser Glu Ser Met Val Gln Arg Ala		
	515	520	525
	Leu Asp Ser Leu Met Lys Gly Arg Thr Thr Leu Val Ile Ala His Arg		
20	530	535	540
	Leu Ser Thr Ile Val Asp Ala Asp Lys Ile Tyr Phe Ile Glu Lys Gly		
	545	550	555
	Glu Ile Thr Gly Ser Gly Lys His Asn Glu Leu Val Ala Thr His Pro		
25	565	570	575
	Leu Tyr Ala Lys Tyr Val Ser Glu Gln Leu Thr Val Gly Gln		
30	580	585	590
	<210> 83		
35	<211> 330		
	<212> PRT		
	<213> Streptomyces peucetius		
	<400> 83		
40	Met Asn Thr Gln Pro Thr Arg Ala Ile Glu Thr Ser Gly Leu Val Lys		
	1	5	10
	15		
45	Val Tyr Asn Gly Thr Arg Ala Val Asp Gly Leu Asp Leu Asn Val Pro		
	20	25	30
	Ala Gly Leu Val Tyr Gly Ile Leu Gly Pro Asn Gly Ala Gly Lys Ser		
50	35	40	45
	Thr Thr Ile Arg Met Leu Ala Thr Leu Leu Arg Pro Asp Gly Gly Thr		
	50	55	60
55	Ala Arg Val Phe Gly His Asp Val Thr Ser Glu Pro Asp Thr Val Arg		
	65	70	75
	80		

Arg Arg Ile Ser Val Thr Gly Gln Tyr Ala Ser Val Asp Glu Gly Leu
 5 85 90 95

Thr Gly Thr Glu Asn Leu Val Met Met Gly Arg Leu Gln Gly Tyr Ser
 100 105 110

Trp Ala Arg Ala Arg Glu Arg Ala Ala Glu Leu Ile Asp Gly Phe Gly
 115 120 125

Leu Gly Asp Ala Arg Asp Arg Leu Leu Lys Thr Tyr Ser Gly Gly Met
 15 130 135 140

Arg Arg Arg Leu Asp Ile Ala Ala Ser Ile Val Val Thr Pro Asp Leu
 145 150 155 160

Leu Phe Leu Asp Glu Pro Thr Thr Gly Leu Asp Pro Arg Ser Arg Asn
 20 165 170 175

Gln Val Trp Asp Ile Val Arg Ala Leu Val Asp Ala Gly Thr Thr Val
 25 180 185 190

Leu Leu Thr Thr Gln Tyr Leu Asp Glu Ala Asp Gln Leu Ala Asp Arg
 195 200 205

Ile Ala Val Ile Asp His Gly Arg Val Ile Ala Glu Gly Thr Thr Gly
 30 210 215 220

Glu Leu Lys Ser Ser Leu Gly Ser Asn Val Leu Arg Leu Arg Leu His
 35 225 230 235 240

Asp Ala Gln Ser Arg Ala Glu Ala Glu Arg Leu Leu Ser Ala Glu Leu
 40 245 250 255

Gly Val Thr Ile His Arg Asp Ser Asp Pro Thr Ala Leu Ser Ala Arg
 260 265 270

Ile Asp Asp Pro Arg Gln Gly Met Arg Ala Leu Ala Glu Leu Ser Arg
 45 275 280 285

Thr His Leu Glu Val Arg Ser Phe Ser Leu Gly Gln Ser Ser Leu Asp
 290 295 300

Glu Val Phe Leu Ala Leu Thr Gly His Pro Ala Asp Asp Arg Ser Thr
 50 305 310 315 320

Glu Glu Ala Ala Glu Glu Lys Val Ala
 55 325 330

<210> 84

5 <211> 569

<212> PRT

<213> Streptomyces coelicolor

10 <400> 84

Met Gln Asn Ala His Arg Ser Asp Thr Gly Ala Ala Ala Leu Thr Gly
1 5 10 1515 Thr Pro Glu Lys Leu Leu Pro Thr Gln Pro Glu Thr Gly Ser Phe Gln
20 25 3020 Val Val Leu Asp Asp Val Val Arg Ala Pro Gly Gly Arg Pro Leu Leu
35 40 45Asp Gly Val Asn Gln Ser Val Ala Leu Gly Glu Arg Val Gly Ile Ile
50 55 6025 Gly Glu Asn Gly Ser Gly Lys Ser Thr Leu Leu Arg Met Leu Ala Gly
65 70 75 8030 Val Asp Arg Pro Asp Gly Gly Gln Val Leu Val Arg Ala Pro Gly Gly
85 90 95Cys Gly Tyr Leu Pro Gln Thr Pro Asp Leu Pro Pro Glu Asp Thr Val
100 105 11035 Gln Asp Ala Ile Asp His Ala Leu Ala Glu Leu Arg Ser Leu Glu Arg
115 120 12540 Gly Leu Arg Glu Ala Glu Gln Ala Leu Ala Gly Ala Glu Pro Glu Glu
130 135 140Leu Glu Gly Leu Leu Gly Ala Tyr Gly Asp Leu Leu Glu Ala Phe Glu
145 150 155 16045 Ala Arg Asp Gly Tyr Ala Ala Asp Ala Arg Val Asp Ala Ala Met His
165 170 175Gly Leu Gly Leu Ala Gly Ile Thr Gly Asp Arg Arg Leu Gly Ser Leu
50 180 185 190Ser Gly Gly Glu Gln Ala Arg Leu Asn Leu Ala Cys Leu Leu Ala Ala
195 200 205

55

EP 1 217 066 A1

Ser Pro Gln Leu Met Leu Leu Asp Glu Pro Thr Asn His Leu Asp Val
 210 215 220

5 Gly Ala Leu Glu Trp Leu Glu Glu Arg Leu Arg Ala His Arg Gly Ser
 225 230 235 240

10 Val Leu Val Val Ser His Asp Arg Val Phe Leu Glu Arg Val Ala Thr
 245 250 255

Ala Leu Trp Glu Val Asp Gly Glu Arg Arg Thr Val Asn Arg His Gly
 260 265 270

15 Gly Gly Tyr Ala Gly Tyr Leu Gln Ala Lys Ala Ala Arg Arg Arg
 275 280 285

20 Trp Glu Gln Ala Tyr Gln Asp Trp Leu Glu Asp Leu Ala Arg Gln Arg
 290 295 300

Glu Leu Ala Arg Ser Ala Ala Asp His Leu Ala Thr Gly Pro Arg Arg
 305 310 315 320

25 Asn Thr Glu Arg Ser Asn Gln Arg His Gln Arg Asn Val Glu Lys Gln
 325 330 335

30 Ile Ser Ala Arg Val Arg Asn Ala Lys Glu Arg Val Arg Arg Leu Glu
 340 345 350

Glu Asn Pro Val Pro Arg Pro Pro Gln Pro Met Arg Phe Arg Ala Arg
 355 360 365

35 Val Glu Gly Gly Thr Val Gly Arg Gly Gly Ala Leu Ala Glu Leu
 370 375 380

40 Tyr Lys Val Thr Val Gly Thr Arg Leu Asp Val Pro Ser Phe Thr Val
 385 390 395 400

45 Asp Pro Gly Glu Arg Ile Leu Ile Thr Gly His Asn Gly Ala Gly Lys
 405 410 415

Ser Thr Leu Leu Arg Val Leu Ala Gly Asp Leu Ala Pro Asp Gln Gly
 420 425 430

50 Glu Cys Glu Arg Pro Glu Arg Ile Gly Trp Leu Pro Gln Glu Thr Glu
 435 440 445

55 Ile Thr Asp Arg Gln Gln Ser Leu Leu Ala Ala Phe Ala Ala Gly Leu
 450 455 460

EP 1 217 066 A1

Pro Gly Ile Ala Glu Glu His Arg Gly Ala Leu Leu Gly Phe Gly Leu
465 470 475 480

5 Phe Arg Pro Ser Ala Leu Gly Thr Ala Val Gly Asp Leu Ser Thr Gly
485 490 495

Gln Leu Arg Arg Leu Ala Leu Ala Arg Leu Leu Arg Asp Pro Ala Asp
10 500 505 510

Leu Leu Leu Leu Asp Glu Pro Thr Asn His Leu Ser Pro Ala Leu Val
15 515 520 525

15 Glu Asp Leu Glu Glu Ala Leu Ala His Tyr Arg Gly Ala Leu Val Val
530 535 540

20 Val Ser His Asp Arg Met Phe Ala Gln Arg Phe Thr Gly Arg Arg Met
545 550 555 560

His Met Glu Gly Gly Arg Phe Val Glu
25 565

<210> 85
30 <211> 1025
<212> PRT
<213> Plasmodium falciparum

<400> 85
35 Met Asp Val Ser Asn Tyr Glu Tyr Leu Arg Ser Tyr Gly Ile Lys Asn
1 5 10 15

Glu Leu Lys Arg Lys Arg Thr His Lys Lys Ile Ile Ile Tyr His Leu
40 20 25 30

Leu Asp Ile Ile Ile Phe Phe Leu Leu Phe Phe Ser Cys Tyr Asn Phe
45 35 40 45

Asn Leu Glu Leu Cys Tyr Lys Tyr Glu Lys Ala Ile Phe Tyr Asn Phe
50 55 60

Phe Lys Ser Ser Val Asp Leu Phe Leu Leu Asn Val Ile Arg Ile Ile
55 65 70 75 80

Tyr Thr Val Ile Leu Phe Arg Leu His Lys Lys Leu Thr Glu Leu Asn
85 90 95

55 Thr Leu Gly Lys Val Tyr Val Leu Ser Arg His Ile Thr Gly Ile Leu

	100	105	110
5	Val Ile Leu Asn Val Ile Lys Met Ile Asn Tyr Ser Tyr Val Ile Lys 115	120	125
10	Ser Glu Asn Pro Leu Tyr Asn Thr Asn Met Tyr Leu Ile Thr Leu Lys 130	135	140
15	Val Leu Phe Met Val Tyr Ser Met Ile Ser Ser Ile Tyr Tyr Tyr Phe 145	150	155
20	Ile Gln Phe Lys Leu Tyr Asn Ile Lys Lys Lys Tyr Ile Ile Ala Arg 165	170	175
25	Val Glu Leu Glu Lys Ile Leu Ile Asn Asp Ile Lys Ser Lys Lys Tyr 180	185	190
30	Asn Ile Tyr Lys Ser Asp Glu Asn Ser Gly Leu Leu Gly Thr Asp Asn 195	200	205
35	Asn Ser Thr Ile Met Asn Asn Glu Tyr Leu Asn Leu Asp Tyr Lys Asn 210	215	220
40	Leu Leu Asp Met Asn Ile Ser Tyr Asn Lys Leu Asn Glu Lys Ile Asn 225	230	235
45	Asn Asp Ile Ile Asn Asn Thr Ser Asp Val Gln Glu Lys Asn Met Asp 245	250	255
50	Tyr Asn Asp Ile His Asn Phe Gln Lys Lys Lys Ser Ser Asn Phe 260	265	/ 270
55	Ala Tyr Leu Asn Phe Phe His Lys Glu Ser Lys Asp Asn Lys Ile Asp 275	280	285
	Val Lys Glu Ser Phe Leu Asn Lys Arg Tyr Gly Ser Asn Lys Arg Ser 290	295	300
	Ser Lys Ile Tyr Asp Asn Asn Asn Asn Asn Asn Asn Asn Ile 305	310	315
	Asn Ser Lys Ile Asp Tyr Leu Glu Asn Asn Ile Thr Tyr Thr Glu Phe 325	330	335
	Lys Lys Ile Leu Leu Pro Tyr Leu Trp Pro Ser Lys Arg Ile Asp Met 340	345	350
	Lys Gly Asn Ser Ser Ile Leu Arg Thr Tyr Ile Val Leu Ile Phe Leu		

	355	360	365	
5	Phe Ile Leu Val Ser Lys Val Phe Ser Val Ile Ser Pro Ile Tyr Leu 370	375	380	
10	Gly Trp Ala Ser Asn Glu Val Leu Lys Lys Ser Leu Ser Ser Ser Val 385	390	395	400
15	Tyr Tyr Leu Gly Leu Tyr Val Thr Phe Phe Phe Ile Ser Lys Phe Leu 405	410	415	
20	Lys Glu Val Cys Gly Val Leu Phe Ser Gln Val Gln Gln Ser Ala Phe 420	425	430	
25	Ile Glu Leu Gln Glu Ser Ile Phe Gln Thr Phe His Asn Leu Ser Tyr 435	440	445	
30	Glu Trp Tyr Ser Ser Lys Asn Ser Gly Gly Ile Met Arg Ile Val Asp 450	455	460	
35	Arg Gly Thr Glu Ser Ala Asn Asn Leu Met Ser Ser Val Leu Met Tyr 465	470	475	480
40	Ile Ile Pro Ala Thr Ile Glu Gly Leu Ile Thr Cys Ile Ile Phe Ile 485	490	495	
45	Phe Lys Tyr Lys Asn Ser Leu Leu Gly Ser Val Leu Phe Ile Gly Leu 500	505	510	
50	Thr Leu Tyr Ile Tyr Ser Thr Ile Lys Ile Thr Lys Trp Arg Lys Lys 515	520	525	
55	Ile Arg Thr Lys Ala Asn Glu Met Asp Asn Val Tyr His Asp Ile Ala 530	535	540	
	His Asp Ser Leu Thr Asn Tyr Glu Asn Val Lys Tyr Phe Ser Asn Glu 545	550	555	560
	Lys Phe Glu Ile Lys Lys Phe Cys Asn Ala Leu Ser Asn Tyr His Arg 565	570	575	
	Tyr Asn Leu Lys Ile Leu Asn Ser Leu Gly Ile Leu Asn Thr Val Gln 580	585	590	
	Gln Phe Ile Leu Asn Gly Thr Leu Phe Phe Thr Leu Leu Cys Val Ile 595	600	605	
	Tyr Met Ile Val Lys Glu Gly Ser Asp Pro Gly Thr Phe Ile Ser Val			

EP 1 217 066 A1

	610	615	620
5	Val Val Tyr Thr Ser Asn Val Phe Ala Pro Leu Ser Ile Leu Gly Thr		
	625	630	635
	Leu Tyr Ala Thr Ile Ile Lys Ser Phe Thr Asp Ile Ser Asp Leu Ile		
10	645	650	655
	Asp Ile Leu Arg Asp Lys Ile Asp Ile Ser Asn Asp Lys Asn Leu Lys		
	660	665	670
15	Asn Phe Asp Leu Thr Ser Gln Glu Lys Lys Phe Gly Val Ser Ile Glu		
	675	680	685
	Phe Asn Asn Val His Phe Asn Tyr Pro Thr Gln Pro Leu His Thr Ser		
20	690	695	700
	Leu Lys Asp Ile Asn Ile Tyr Ile Lys Pro Gly Thr Thr Cys Ala Leu		
	705	710	715
	720		
25	Val Gly His Thr Gly Ser Gly Lys Thr Thr Ile Ser Lys Leu Leu Tyr		
	725	730	735
	Arg Phe Tyr Asp Ser Lys Gly Glu Ile Lys Ile Gly Gly Arg Asn Ile		
30	740	745	750
	Asn Glu Tyr Thr Arg Asn Ser Ile Arg Asn Ile Ile Gly Ile Val Pro		
	755	760	765
35	Gln Asp Thr Ile Leu Phe Asn Glu Ser Ile Lys Tyr Asn Ile Leu Tyr		
	770	775	780
	Gly Lys Leu Asp Ala Thr Glu Glu Leu Ile Gln Ala Val Lys Ser		
40	785	790	795
	800		
	Ala Gln Leu Tyr Asp Phe Ile Gln Ser Leu Pro Lys Lys Trp Asp Thr		
	805	810	815
45	Leu Val Gly Asp Lys Gly Val Lys Leu Ser Gly Gly Glu Arg Gln Arg		
	820	825	830
	Ile Ser Ile Ala Arg Cys Leu Leu Lys Asp Pro Lys Ile Val Ile Phe		
50	835	840	845
	Asp Glu Ala Thr Ser Ser Leu Asp Ser Arg Thr Glu Tyr Leu Phe Gln		
	850	855	860
55	Lys Ala Val Glu Asp Leu Arg Lys Asn Arg Thr Ile Ile Ile Ala		

EP 1 217 066 A1

865	870	875	880
His Lys Leu Cys Thr Ile Thr Thr Ala Glu Leu Ile Ile Leu Leu Asn			
5	885	890	895
Lys Gly Lys Ile Ile Glu Arg Gly Thr His Leu Asp Leu Leu Lys Cys			
900 905 910			
10	Asn Gly Glu Tyr Thr Glu Met Trp Asn Met Gln Ser Lys Ser Asn Glu		
	915	920	925
15	Pro His Thr Glu Thr Asn Ser Ser Ile Asp Lys Asp Asp Val Asn Lys		
	930	935	940
Asn Asn Asn Lys Asn Asn Asp Val Ile Leu Asn Thr Cys Lys Asn Asp			
20	945	950	955 960
Ile Thr Thr Ser Phe Arg Ser Asn Ser Glu Lys Ser Ser Gln Glu Phe			
	965	970	975
25	Ser Asp Ala Ser Asn His Ile Lys Gln Ser Lys Thr Ser Asn Asp His		
	980	985	990
Asn Asn Asn Ile Asn Val His Lys Lys Asn Glu Gln Glu Gln Leu Phe			
30	995	1000	1005
Leu Thr Asn Asp Lys Thr Asp Met Asp Asp Asn Met Asn Asn Lys Lys			
	1010	1015	1020
35	Lys		
	1025		
40			
<210> 86			
<211> 1419			
<212> PRT			
<213> Plasmodium falciparum			
45	<400> 86		
	Met Gly Lys Glu Gln Lys Glu Lys Lys Asp Gly Asn Leu Ser Ile Lys		
	1	5	10 15
50	Glu Glu Val Glu Lys Glu Leu Asn Lys Lys Ser Thr Ala Glu Leu Phe		
	20	25	30
55	Arg Lys Ile Lys Asn Glu Lys Ile Ser Phe Phe Leu Pro Phe Lys Cys		
	35	40	45

Leu Pro Ala Gln His Arg Lys Leu Leu Phe Ile Ser Phe Val Cys Ala
 5 50 55 60

Val Leu Ser Gly Gly Thr Leu Pro Phe Phe Ile Ser Val Phe Gly Val
 10 65 70 75 80

Ile Leu Lys Asn Met Asn Leu Gly Asp Asp Ile Asn Pro Ile Ile Leu
 15 85 90 95

Ser Leu Val Ser Ile Gly Leu Val Gln Phe Ile Leu Ser Met Ile Ser
 20 100 105 110

Ser Tyr Cys Met Asp Val Ile Thr Ser Lys Ile Leu Lys Thr Leu Lys
 25 115 120 125

Leu Glu Tyr Leu Arg Ser Val Phe Tyr Gln Asp Gly Gln Phe His Asp
 30 130 135 140

Asn Asn Pro Gly Ser Lys Leu Arg Ser Asp Leu Asp Phe Tyr Leu Glu
 35 145 150 155 160

Gln Val Ser Ser Gly Ile Gly Thr Lys Phe Ile Thr Ile Phe Thr Tyr
 40 165 170 175

Ala Ser Ser Phe Leu Gly Leu Tyr Ile Trp Ser Leu Ile Lys Asn Ala
 45 180 185 190

Arg Leu Thr Leu Cys Ile Thr Cys Val Phe Pro Leu Ile Tyr Val Cys
 50 195 200 205

Gly Val Ile Cys Asn Lys Lys Val Lys Leu Asn Lys Lys Thr Ser Leu
 55 210 215 220

Leu Tyr Asn Asn Asn Thr Met Ser Ile Ile Glu Glu Ala Leu Met Gly
 60 225 230 235 240

Ile Arg Thr Val Ala Ser Tyr Cys Gly Glu Lys Thr Ile Leu Asn Lys
 65 245 250 255

Phe Asn Leu Ser Glu Thr Phe Tyr Ser Lys Tyr Ile Leu Lys Ala Asn
 70 260 265 270

Phe Val Glu Ala Leu His Ile Gly Leu Ile Asn Gly Leu Ile Leu Val
 75 275 280 285

Ser Tyr Ala Phe Gly Phe Trp Tyr Gly Thr Arg Ile Ile Ile Asn Ser
 80 290 295 300

Ala Thr Asn Gln Tyr Pro Asn Asn Asp Phe Asn Gly Ala Ser Val Ile
 305 310 315 320
 5

Ser Ile Leu Leu Gly Val Leu Ile Ser Met Phe Met Leu Thr Ile Ile
 325 330 335

10 Leu Pro Asn Ile Thr Glu Tyr Met Lys Ala Leu Glu Ala Thr Asn Ser
 340 345 350

15 Leu Tyr Glu Ile Ile Asn Arg Lys Pro Leu Val Glu Asn Asn Asp Asp
 355 360 365

Gly Glu Thr Leu Pro Asn Ile Lys Lys Ile Glu Phe Lys Asn Val Arg
 370 375 380

20 Phe His Tyr Asp Thr Arg Lys Asp Val Glu Ile Tyr Lys Asp Leu Ser
 385 390 395 400

25 Phe Thr Leu Lys Glu Gly Lys Thr Tyr Ala Phe Val Gly Glu Ser Gly
 405 410 415

Cys Gly Lys Ser Thr Ile Leu Lys Leu Ile Glu Arg Leu Tyr Asp Pro
 420 425 430

30 Thr Glu Gly Asp Ile Ile Val Asn Asp Ser His Asn Leu Lys Asp Ile
 435 440 445

35 Asn Leu Lys Trp Trp Arg Ser Lys Ile Gly Val Val Ser Gln Asp Pro
 450 455 460

Leu Leu Phe Ser Asn Ser Ile Lys Asn Asn Ile Lys Tyr Ser Leu Tyr
 465 470 475 480

40 Ser Leu Lys Asp Leu Glu Ala Met Glu Asn Tyr Tyr Glu Glu Asn Thr
 485 490 495

45 Asn Asp Thr Tyr Glu Asn Lys Asn Phe Ser Leu Ile Ser Asn Ser Met
 500 505 510

Thr Ser Asn Glu Leu Leu Glu Met Lys Lys Glu Tyr Gln Thr Ile Lys
 515 520 525

50 Asp Ser Asp Val Val Asp Val Ser Lys Lys Val Leu Ile His Asp Phe
 530 535 540

55 Val Ser Ser Leu Pro Asp Lys Tyr Asp Thr Leu Val Gly Ser Asn Ala
 545 550 555 560

EP 1 217 066 A1

Ser Lys Leu Ser Gly Gly Gln Lys Gln Arg Ile Ser Ile Ala Arg Ala
5 565 570 575

Ile Met Arg Asn Pro Lys Ile Leu Ile Leu Asp Glu Ala Thr Ser Ser
10 580 585 590

Leu Asp Asn Lys Ser Glu Tyr Leu Val Gln Lys Thr Ile Asn Asn Leu
15 595 600 605

Lys Gly Asn Glu Asn Arg Ile Thr Ile Ile Ala His Arg Leu Ser
20 610 615 620

Thr Ile Arg Tyr Ala Asn Thr Ile Phe Val Leu Ser Asn Arg Glu Arg
25 625 630 635 640

Ser Asp Asn Asn Asn Asn Asn Asn Asp Asp Asn Asn Asn Asn Asn
30 645 650 655

Asn Asn Asn Asn Lys Ile Asn Asn Glu Gly Ser Tyr Ile Ile Glu
35 660 665 670

Gln Gly Thr His Asp Ser Leu Met Lys Asn Lys Asn Gly Ile Tyr His
40 675 680 685

Leu Met Ile Asn Asn Gln Lys Ile Ser Ser Asn Lys Ser Ser Asn Asn
45 690 695 700

Gly Asn Asp Asn Gly Ser Asp Asn Lys Ser Ser Ala Tyr Lys Asp Ser
50 705 710 715 720

Asp Thr Gly Asn Asp Ala Asp Asn Met Asn Ser Leu Ser Ile His Glu
55 725 730 735

Asn Glu Asn Ile Ser Asn Asn Arg Asn Cys Lys Asn Thr Ala Glu Asn
60 740 745 750

Glu Lys Glu Glu Lys Val Pro Phe Phe Lys Arg Met Phe Arg Arg Lys
65 755 760 765

Lys Lys Ala Pro Asn Asn Leu Arg Ile Ile Tyr Lys Glu Ile Phe Ser
70 770 775 780

Tyr Lys Lys Asp Val Thr Ile Ile Phe Phe Ser Ile Leu Val Ala Gly
75 785 790 795 800

Gly Leu Tyr Pro Val Phe Ala Leu Leu Tyr Ala Arg Tyr Val Ser Thr
80 805 810 815

EP 1 217 066 A1

Leu Phe Asp Phe Ala Asn Leu Glu Tyr Asn Ser Asn Lys Tyr Ser Ile
 5 820 825 830

Tyr Ile Leu Leu Ile Ala Ile Ala Met Phe Ile Ser Glu Thr Leu Lys
 835 840 845

10 Asn Tyr Tyr Asn Asn Lys Ile Gly Glu Lys Val Glu Lys Thr Met Lys
 850 855 860

Arg Arg Leu Phe Glu Asn Ile Leu Tyr Gln Glu Met Ser Phe Phe Asp
 15 865 870 875 880

Gln Asp Lys Asn Thr Pro Gly Val Leu Ser Ala His Ile Asn Arg Asp
 885 890 895

20 Val His Leu Leu Lys Thr Gly Leu Val Asn Asn Ile Val Ile Phe Ser
 900 905 910

His Phe Ile Met Leu Phe Leu Val Ser Met Val Met Ser Phe Tyr Phe
 25 915 920 925

Cys Pro Ile Val Ala Ala Val Leu Thr Phe Ile Tyr Phe Ile Asn Met
 930 935 940

30 Arg Val Phe Ala Val Arg Ala Arg Leu Thr Lys Ser Lys Glu Ile Glu
 945 950 955 960

Lys Lys Glu Asn Met Ser Ser Gly Val Phe Ala Phe Ser Ser Asp Asp
 35 965 970 975

Glu Met Phe Lys Asp Pro Ser Phe Leu Ile Gln Glu Ala Phe Tyr Asn
 980 985 990

40 Met His Thr Val Ile Asn Tyr Gly Leu Glu Asp Tyr Phe Cys Asn Leu
 995 1000 1005

Ile Glu Lys Ala Ile Asp Tyr Lys Asn Lys Gly Gln Lys Arg Arg Ile
 45 1010 1015 1020

Ile Val Asn Ala Ala Leu Trp Gly Phe Ser Gln Ser Ala Gln Leu Phe
 1025 1030 1035 1040

50 Ile Asn Ser Phe Ala Tyr Trp Phe Gly Ser Phe Leu Ile Lys Arg Gly
 1045 1050 1055

Thr Ile Leu Val Asp Asp Phe Met Lys Ser Leu Phe Thr Phe Ile Phe
 55 1060 1065 1070

5 Thr Gly Ser Tyr Ala Gly Lys Leu Met Ser Leu Lys Gly Asp Ser Glu
 1075 1080 1085

 10 Asn Ala Lys Leu Ser Phe Glu Lys Tyr Tyr Pro Leu Met Ile Arg Lys
 1090 1095 1100

 15 Ser Asn Ile Asp Val Arg Asp Asp Gly Gly Ile Arg Ile Asn Lys Asn
 1105 1110 1115 1120

 20 Leu Ile Lys Gly Lys Val Asp Ile Lys Asp Val Asn Phe Arg Tyr Ile
 1125 1130 1135

 25 Ser Arg Pro Asn Val Pro Ile Tyr Lys Asn Leu Ser Phe Thr Cys Asp
 1140 1145 1150

 30 Ser Lys Lys Thr Thr Ala Ile Val Gly Glu Thr Gly Ser Gly Lys Ser
 1155 1160 1165

 35 Thr Phe Met Asn Leu Leu Leu Arg Phe Tyr Asp Leu Lys Asn Asp His
 1170 1175 1180

 40 Ile Ile Leu Lys Asn Asp Met Thr Asn Phe Gln Asp Tyr Gln Asn Asn
 1185 1190 1195 1200

 45 Asn Asn Asn Ser Leu Val Leu Lys Asn Val Asn Glu Phe Ser Asn Gln
 1205 1210 1215

 50 Ser Gly Ser Ala Glu Asp Tyr Thr Val Phe Asn Asn Asn Gly Glu Ile
 1220 1225 1230

 55 Leu Leu Asp Asp Ile Asn Ile Cys Asp Tyr Asn Leu Arg Asp Leu Arg
 1235 1240 1245

 60 Asn Leu Phe Ser Ile Val Ser Gln Glu Pro Met Leu Phe Asn Met Ser
 1250 1255 1260

 65 Ile Tyr Glu Asn Ile Lys Phe Gly Arg Glu Asp Ala Thr Leu Glu Asp
 1265 1270 1275 1280

 70 Val Lys Arg Val Ser Lys Phe Ala Ala Ile Asp Glu Phe Ile Glu Ser
 1285 1290 1295

 75 Leu Pro Asn Lys Tyr Asp Thr Asn Val Gly Pro Tyr Gly Lys Ser Leu
 1300 1305 1310

 80 Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Leu Leu Arg
 1315 1320 1325

Glu Pro Lys Ile Leu Leu Leu Asp Glu Ala Thr Ser Ser Leu Asp Ser
 1330 1335 1340
 5

Asn Ser Glu Lys Leu Ile Glu Lys Thr Ile Val Asp Ile Lys Asp Lys
 1345 1350 1355 1360

10 Ala Asp Lys Thr Ile Ile Thr Ile Ala His Arg Ile Ala Ser Ile Lys
 1365 1370 1375

15 Arg Ser Asp Lys Ile Val Val Phe Asn Asn Pro Asp Arg Asn Gly Thr
 1380 1385 1390

20 Phe Val Gln Ser His Gly Thr His Asp Glu Leu Leu Ser Ala Gln Asp
 1395 1400 1405

25 Gly Ile Tyr Lys Lys Tyr Val Lys Leu Ala Lys
 1410 1415

30 <210> 87
 <211> 1548
 <212> PRT
 <213> Leishmania tarentolae

35 <400> 87
 Met Val Asp Asn Gly His Val Thr Ile Ala Met Ala Asp Leu Gly Thr
 1 5 10 15

40 Val Val Glu Ile Ala Gln Val Arg Cys Gln Gln Glu Ala Gln Arg Lys
 20 25 30

45 Phe Ala Glu Gln Leu Asp Glu Leu Trp Gly Gly Glu Pro Ala Tyr Thr
 35 40 45

Pro Thr Val Glu Asp Gln Ala Ser Trp Phe Gln Gln Leu Tyr Tyr Gly
 50 55 60

50 Trp Ile Gly Asp Tyr Ile Tyr Lys Ala Ala Ala Gly Asn Ile Thr Glu
 65 70 75 80

55 Ala Asp Leu Pro Pro Pro Thr Arg Ser Thr Arg Thr Tyr His Ile Gly
 85 90 95

Arg Lys Leu Ser Arg Gln Ala His Ala Asp Ile Asp Ala Ser Arg Arg
 100 105 110

EP 1 217 066 A1

Trp Gln Gly Tyr Ile Gly Cys Glu Val Val Tyr Lys Ser Glu Ala Glu
115 120 125

5 Ala Lys Gly Val Leu Arg Trp Val Gly His Leu Gln Gln Ser Asp Tyr
130 135 140

10 Pro Arg Ser Leu Val Ala Gly Val Glu Trp Arg Met Pro Pro Arg His
145 150 155 160

Arg Arg Leu Ala Val Leu Gly Ser Ala Ala Ala Leu His Asn Gly Val
165 170 175

15 Val His Gly Glu Arg Leu Phe Trp Pro His Glu Asp Asn Tyr Leu Cys
180 185 190

20 Ser Cys Glu Pro Val Glu Gln Leu Tyr Val Lys Ser Lys Tyr Asn Leu
195 200 205

Ile Pro Pro Arg Pro Pro Pro Ser Pro Asp Leu Leu Arg Thr Leu Phe
210 215 220

25 Lys Val His Trp Tyr His Val Trp Ala Gln Ile Leu Pro Lys Leu Leu
225 230 235 240

Ser Asp Val Thr Ala Leu Met Leu Pro Val Leu Leu Glu Tyr Phe Val
245 250 255

30 Lys Tyr Leu Asn Ala Asp Asn Ala Thr Trp Gly Trp Gly Leu Gly Leu
260 265 270

35 Ala Leu Thr Ile Phe Leu Thr Asn Val Ile Gln Ser Cys Ser Ala His
275 280 285

40 Lys Tyr Asp His Ile Ser Ile Arg Thr Ala Ala Leu Phe Glu Thr Ser
290 295 300

Ser Met Ala Leu Leu Phe Glu Lys Cys Phe Thr Val Ser Arg Arg Ser
305 310 315 320

45 Leu Gln Arg Pro Asp Met Ser Val Gly Arg Ile Met Asn Met Val Gly
325 330 335

50 Asn Asp Val Asp Asn Ile Gly Ser Leu Asn Trp Tyr Val Met Tyr Phe
340 345 350

55 Trp Ser Ala Pro Leu Gln Leu Val Leu Cys Leu Leu Leu Ile Arg
355 360 365

EP 1 217 066 A1

	Leu Val Gly Trp Leu Arg Val Pro Gly Met Ala Val Leu Phe Val Thr			
5	370	375	380	
	Leu Pro Leu Gln Ala Val Ile Ser Lys His Val Gln Asp Val Ser Glu			
	385	390	395	400
10	Arg Met Ala Ser Val Val Asp Leu Arg Ile Lys Arg Thr Asn Glu Leu			
	405	410	415	
	Leu Ser Gly Val Arg Ile Val Lys Phe Met Gly Trp Glu Pro Val Phe			
15	420	425	430	
	Leu Ala Arg Ile Gln Asp Ala Arg Ser Arg Glu Leu Arg Cys Leu Arg			
	435	440	445	
20	Asp Val His Val Ala Asn Val Phe Phe Met Phe Val Asn Asp Ala Thr			
	450	455	460	
	Pro Thr Leu Val Ile Ala Val Val Phe Ile Leu Tyr His Val Ser Gly			
25	465	470	475	480
	Lys Val Leu Lys Pro Glu Val Val Phe Pro Thr Ile Ala Leu Leu Asn			
	485	490	495	
30	Thr Met Arg Val Ser Phe Phe Met Ile Pro Ile Ile Ile Ser Ser Ile			
	500	505	510	
	Leu Gln Cys Phe Val Ser Ala Lys Arg Val Thr Ala Phe Ile Glu Cys			
35	515	520	525	
	Pro Asp Thr His Ser Gln Val Gln Asp Ile Ala Ser Ile Asp Val Pro			
	530	535	540	
40	Asp Ala Ala Ala Ile Phe Lys Gly Ala Ser Ile His Thr Tyr Leu Pro			
	545	550	555	560
	Val Lys Leu Pro Arg Cys Lys Ser Arg Leu Thr Ala Met Gln Arg Ser			
45	565	570	575	
	Thr Leu Trp Phe Arg Arg Arg Gly Val Pro Glu Thr Glu Trp Tyr Glu			
	580	585	590	
50	Val Asp Ser Pro Asp Ala Ser Ala Ser Ser Leu Ala Val His Ser Thr			
	595	600	605	
	Thr Val His Met Gly Ser Thr Gln Thr Val Ile Thr Asp Ser Asp Gly			
55	610	615	620	

EP 1217066 A1

Ala Ala Gly Glu Asp Glu Lys Gly Glu Val Glu Glu Gly Asp Arg Glu
625 630 635 640

5 Tyr Tyr Gln Leu Val Ser Lys Glu Leu Leu Arg Asn Val Ser Leu Thr
645 650 655

Ile Pro Lys Gly Lys Leu Thr Met Val Ile Gly Ser Thr Gly Ser Gly
10 660 665 670

Lys Ser Thr Leu Leu Gly Ala Leu Met Gly Glu Tyr Ser Val Glu Ser
675 680 685

Gly Glu Leu Trp Ala Glu Arg Ser Ile Ala Tyr Val Pro Gln Gln Ala
15 690 695 700

Trp Ile Met Asn Ala Thr Leu Arg Gly Asn Ile Leu Phe Phe Asp Glu
20 705 710 715 720

Glu Arg Ala Glu Asp Leu Gln Asp Val Ile Arg Cys Cys Gln Leu Glu
725 730 735

25 Ala Asp Leu Ala Gln Phe Cys Gly Gly Leu Asp Thr Glu Ile Gly Glu
740 745 750

Met Gly Val Asn Leu Ser Gly Gly Gln Lys Ala Arg Val Ser Leu Ala
30 755 760 765

Arg Ala Val Tyr Ala Asn Arg Asp Val Tyr Leu Leu Asp Asp Pro Leu
770 775 780

35 Ser Ala Leu Asp Ala His Val Gly Gln Arg Ile Val Gln Asp Val Ile
785 790 795 800

Leu Gly Arg Leu Arg Gly Lys Thr Arg Val Leu Ala Thr His Gln Ile
40 805 810 815

His Leu Leu Pro Leu Ala Asp Tyr Ile Val Val Leu Gln His Gly Ser
820 825 830

Ile Val Phe Ala Gly Asp Phe Ala Ala Phe Ser Ala Thr Ala Leu Glu
45 835 840 845

Glu Thr Leu Arg Gly Glu Leu Lys Gly Ser Lys Asp Val Glu Ser Cys
50 850 855 860

Ser Ser Asp Val Asp Thr Glu Ser Ala Thr Ala Glu Thr Ala Pro Tyr
865 870 875 880

EP 1 217 066 A1

Val Ala Lys Ala Lys Gly Leu Asn Ala Glu Gln Glu Thr Ser Leu Ala
885 890 895

5 Gly Gly Glu Asp Pro Leu Arg Ser Asp Val Glu Ala Gly Arg Leu Met
900 905 910

10 Thr Thr Glu Glu Lys Ala Thr Gly Lys Val Pro Trp Ser Thr Tyr Val
915 920 925

15 Ala Tyr Leu Lys Ser Cys Gly Gly Leu Glu Ala Trp Gly Cys Leu Leu
930 935 940

20 Ala Thr Phe Ala Leu Thr Glu Cys Val Thr Ala Ala Ser Ser Val Trp
945 950 955 960

Leu Ser Ile Trp Ser Thr Gly Ser Leu Met Trp Ser Ala Asp Thr Tyr
965 970 975

25 Leu Tyr Val Tyr Leu Phe Ile Val Phe Leu Glu Ile Phe Gly Ser Pro
980 985 990

Leu Arg Phe Phe Leu Cys Tyr Tyr Leu Ile Arg Ile Gly Ser Arg Asn
995 1000 1005

30 Met His Arg Asp Leu Leu Glu Ser Ile Gly Val Ala Arg Met Ser Phe
1010 1015 1020

Phe Asp Thr Thr Pro Val Gly Arg Val Leu Asn Arg Phe Thr Lys Asp
1025 1030 1035 1040

35 Met Ser Ile Leu Asp Asn Thr Leu Asn Asp Gly Tyr Leu Tyr Leu Leu
1045 1050 1055

40 Glu Tyr Phe Phe Ser Met Cys Ser Thr Val Ile Ile Met Val Val Val
1060 1065 1070

Gln Pro Phe Val Leu Val Ala Ile Val Pro Cys Val Tyr Ser Tyr Tyr
45 1075 1080 1085

Lys Leu Met Gln Val Tyr Asn Ala Ser Asn Arg Glu Thr Arg Arg Ile
1090 1095 1100

50 Lys Ser Ile Ala His Ser Pro Val Phe Thr Leu Leu Glu Glu Ser Leu
1105 1110 1115 1120

Gln Gly Gln Arg Thr Ile Ala Thr Tyr Gly Lys Leu His Leu Val Leu
55 1125 1130 1135

EP 1217066 A1

Gln Glu Ala Leu Gly Arg Leu Asp Val Val Tyr Ser Ala Leu Tyr Met
 1140 1145 1150

5 Gln Asn Val Ser Asn Arg Trp Leu Gly Val Arg Leu Glu Phe Leu Ser
 1155 1160 1165

Cys Val Val Thr Phe Met Val Ala Phe Ile Gly Val Ile Gly Lys Met
 10 1170 1175 1180

Glu Gly Ala Ser Ser Gln Asn Ile Gly Leu Ile Ser Leu Ser Leu Thr
 1185 1190 1195 1200

15 Met Ser Met Thr Leu Thr Glu Thr Leu Asn Trp Leu Val Arg Gln Val
 1205 1210 1215

Ala Met Val Glu Ala Asn Met Asn Ser Val Glu Arg Val Leu His Tyr
 20 1220 1225 1230

Thr Gln Glu Val Glu His Glu His Val Pro Glu Met Gly Glu Leu Val
 1235 1240 1245

25 Ala Gln Leu Val Arg Ser Glu Ser Gly Arg Gly Ala Asn Val Thr Glu
 1250 1255 1260

Thr Val Val Ile Glu Ser Ala Gly Ala Ala Ser Ser Ala Leu His Pro
 30 1265 1270 1275 1280

Val Gln Ala Gly Ser Leu Val Leu Glu Gly Val Gln Met Arg Tyr Arg
 1285 1290 1295

35 Glu Gly Leu Pro Leu Val Leu Arg Gly Val Ser Phe Gln Ile Ala Pro
 1300 1305 1310

Arg Glu Lys Val Gly Ile Val Gly Arg Thr Gly Ser Gly Lys Ser Thr
 40 1315 1320 1325

Leu Leu Leu Thr Phe Met Arg Met Val Glu Val Cys Gly Gly Val Ile
 45 1330 1335 1340

His Val Asn Gly Arg Glu Met Ser Ala Tyr Gly Leu Arg Glu Leu Arg
 1345 1350 1355 1360

Arg His Phe Ser Met Ile Pro Gln Asp Pro Val Leu Phe Asp Gly Thr
 50 1365 1370 1375

Val Arg Gln Asn Val Asp Pro Phe Leu Glu Ala Ser Ser Ala Glu Val
 55 1380 1385 1390

EP 1 217 066 A1

Trp Ala Ala Leu Glu Leu Val Gly Leu Arg Glu Arg Val Ala Ser Glu
1395 1400 1405

5 Ser Glu Gly Ile Asp Ser Arg Val Leu Glu Gly Gly Ser Asn Tyr Ser
1410 1415 1420

10 Val Gly Gln Arg Gln Leu Met Cys Met Ala Arg Ala Leu Leu Lys Arg
1425 1430 1435 1440

Gly Ser Gly Phe Ile Leu Met Asp Glu Ala Thr Ala Asn Ile Asp Pro
1445 1450 1455

15 Ala Leu Asp Arg Gln Ile Gln Ala Thr Val Met Ser Ala Phe Ser Ala
1460 1465 1470

20 Tyr Thr Val Ile Thr Ile Ala His Arg Leu His Thr Val Ala Gln Tyr
1475 1480 1485

Asp Lys Ile Ile Val Met Asp His Gly Val Val Ala Glu Met Gly Ser
1490 1495 1500

25 Pro Arg Glu Leu Val Met Asn His Gln Ser Met Phe His Ser Met Val
1505 1510 1515 1520

30 Glu Ser Leu Gly Ser Arg Gly Ser Lys Asp Phe Tyr Glu Leu Leu Met
1525 1530 1535

35 Gly Arg Arg Ile Val Gln Pro Ala Val Leu Ser Asp
1540 1545

40 <210> 88
<211> 1530
<212> PRT
<213> Schizosaccharomyces pombe

45 <400> 88
Met Asn Gln Asn Ser Asp Thr Thr His Gly Gln Ala Leu Gly Ser Thr
1 5 10 15

50 Leu Asn His Thr Thr Glu Val Thr Arg Ile Ser Asn Ser Ser Asp His
20 25 30

Phe Glu Asp Ser Ser Ser Asn Val Asp Glu Ser Leu Asp Ser Ser Asn
35 40 45

55 Pro Ser Ser Asn Glu Lys Ala Ser His Thr Asn Glu Glu Tyr Arg Ser

EP 1 217 066 A1

	50	55	60
5	Lys Gly Asn Gln Ser Tyr Val Pro Ser Ser Ser Asn Glu Pro Ser Pro		
	65	70	75
	80		
	Glu Ser Ser Ser Asn Ser Asp Ser Ser Ser Asp Asp Ser Ser Val		
10	85	90	95
	Asp Arg Leu Ala Gly Asp Pro Phe Glu Leu Gly Glu Asn Phe Asn Leu		
	100	105	110
15	Lys His Tyr Leu Arg Ala Tyr Lys Asp Ser Leu Gln Arg Asp Asp Ile		
	115	120	125
	Ile Thr Arg Ser Ser Gly Val Cys Met Arg Asp His Ser Val Tyr Gly		
20	130	135	140
	Val Gly Ser Gly Tyr Glu Phe Leu Lys Thr Phe Pro Asp Ile Phe Leu		
	145	150	155
	160		
25	Gln Pro Tyr Arg Ala Ile Thr Glu Lys Gln Val Val Glu Lys Ala Ile		
	165	170	175
	Leu Ser His Cys His Ala Leu Ala Asn Ala Gly Glu Leu Val Met Val		
30	180	185	190
	Leu Gly Gln Pro Gly Ser Gly Cys Ser Thr Phe Leu Arg Ser Val Thr		
	195	200	205
35	Ser Asp Thr Val His Tyr Lys Arg Val Glu Gly Thr Thr His Tyr Asp		
	210	215	220
	Gly Ile Asp Lys Ala Asp Met Lys Lys Phe Phe Pro Gly Asp Leu Leu		
40	225	230	235
	240		
	Tyr Ser Gly Glu Asn Asp Val His Phe Pro Ser Leu Thr Thr Ala Glu		
	245	250	255
45	Thr Leu Asp Phe Ala Ala Lys Cys Arg Thr Pro Asn Asn Arg Pro Cys		
	260	265	270
	Asn Leu Thr Arg Gln Glu Tyr Val Ser Arg Glu Arg His Leu Ile Ala		
50	275	280	285
	Thr Ala Phe Gly Leu Thr His Thr Phe Asn Thr Lys Val Gly Asn Asp		
	290	295	300
55	Phe Val Arg Gly Val Ser Gly Gly Glu Arg Lys Arg Val Thr Ile Ser		

EP 1 217 066 A1

	305	310	315	320
5	Glu Gly Phe Ala Thr Arg Pro Thr Ile Ala Cys Trp Asp Asn Ser Thr			
	325	330	335	
	Arg Gly Leu Asp Ser Ser Thr Ala Phe Glu Phe Val Asn Val Leu Arg			
10	340	345	350	
	Thr Cys Ala Asn Glu Leu Lys Met Thr Ser Phe Val Thr Ala Tyr Gln			
	355	360	365	
15	Ala Ser Glu Lys Ile Tyr Lys Leu Phe Asp Arg Ile Cys Val Leu Tyr			
	370	375	380	
	Ala Gly Arg Gln Ile Tyr Tyr Gly Pro Ala Asp Lys Ala Lys Gln Tyr			
20	385	390	395	400
	Phe Leu Asp Met Gly Phe Asp Cys His Pro Arg Glu Thr Thr Pro Asp			
	405	410	415	
25	Phe Leu Thr Ala Ile Ser Asp Pro Lys Ala Arg Phe Pro Arg Lys Gly			
	420	425	430	
	Phe Glu Asn Arg Val Pro Arg Thr Pro Asp Glu Phe Glu Gln Met Trp			
30	435	440	445	
	Arg Asn Ser Ser Val Tyr Ala Asp Leu Met Ala Glu Met Glu Ser Tyr			
	450	455	460	
35	Asp Lys Arg Trp Thr Glu Thr Thr Pro Ala Ser Ser Glu Ala Pro Glu			
	465	470	475	480
	Lys Asp Asn Phe Gly Ser Asp Ile Ser Ala Thr Thr Lys His Glu Leu			
40	485	490	495	
	Tyr Arg Gln Ser Ala Val Ala Glu Lys Ser Lys Arg Val Lys Asp Thr			
	500	505	510	
45	Ser Pro Tyr Thr Val Thr Phe Ser Gln Gln Leu Trp Tyr Cys Leu Ala			
	515	520	525	
	Arg Ser Trp Glu Arg Tyr Ile Asn Asp Pro Ala Tyr Ile Gly Ser Met			
50	530	535	540	
	Ala Phe Ala Phe Leu Phe Gln Ser Leu Ile Ile Gly Ser Ile Phe Tyr			
	545	550	555	560
55	Asp Met Lys Leu Asn Thr Val Asp Val Phe Ser Arg Gly Gly Val Leu			

EP 1 217 066 A1

	565	570	575
5	Phe Phe Ser Ile Leu Phe Cys Ala Leu Gln Ser Leu Ser Glu Ile Ala 580	585	590
	Asn Met Phe Ser Gln Arg Pro Ile Ile Ala Lys His Arg Ala Ser Ala 595	600	605
10	Leu Tyr His Pro Ala Ala Asp Val Ile Ser Ser Leu Ile Val Asp Leu 610	615	620
15	Pro Phe Arg Phe Ile Asn Ile Ser Val Phe Ser Ile Val Leu Tyr Phe 625	630	635
	Leu Thr Asn Leu Lys Arg Thr Ala Gly Gly Phe Trp Thr Tyr Phe Leu 645	650	655
20	Phe Leu Phe Ile Gly Ala Thr Cys Met Ser Ala Phe Phe Arg Ser Leu 660	665	670
	Ala Gly Ile Met Pro Asn Val Glu Ser Ala Ser Ala Leu Gly Gly Ile 675	680	685
	Gly Val Leu Ala Ile Ala Ile Tyr Thr Gly Tyr Ala Ile Pro Asn Ile 690	695	700
30	Asp Val Gly Trp Trp Phe Arg Trp Ile Ala Tyr Leu Asp Pro Leu Gln 705	710	715
	Phe Gly Phe Glu Ser Leu Met Ile Asn Glu Phe Lys Ala Arg Gln Phe 725	730	735
40	Glu Cys Ser Gln Leu Ile Pro Tyr Gly Ser Gly Tyr Asp Asn Tyr Pro 740	745	750
	Val Ala Asn Lys Ile Cys Pro Val Thr Ser Ala Glu Pro Gly Thr Asp 755	760	765
45	Tyr Val Asp Gly Ser Thr Tyr Leu Tyr Ile Ser Phe Asn Tyr Lys Thr 770	775	780
	Arg Gln Leu Trp Arg Asn Leu Ala Ile Ile Gly Tyr Tyr Ala Phe 785	790	795
	Leu Val Phe Val Asn Ile Val Ala Ser Glu Thr Leu Asn Phe Asn Asp 805	810	815
55	Leu Lys Gly Glu Tyr Leu Val Phe Arg Arg Gly His Ala Pro Asp Ala		

EP 1 217 066 A1

	820	825	830
5	Val Lys Ala Ala Val Asn Glu Gly Gly Lys Pro Leu Asp Leu Glu Thr 835	840	845
	Gly Gln Asp Thr Gln Gly Gly Asp Val Val Lys Glu Ser Pro Asp Asn 850	855	860
10	Glu Glu Glu Leu Asn Lys Glu Tyr Glu Gly Ile Glu Lys Gly His Asp 865	870	875
	Ile Phe Ser Trp Arg Asn Leu Asn Tyr Asp Ile Gln Ile Lys Gly Glu 885	890	895
15	His Arg Arg Leu Leu Asn Gly Val Gln Gly Phe Val Val Pro Gly Lys 900	905	910
20	Leu Thr Ala Leu Met Gly Glu Ser Gly Ala Gly Lys Thr Thr Leu Leu 915	920	925
	Asn Val Leu Ala Gln Arg Val Asp Thr Gly Val Val Thr Gly Asp Met 930	935	940
25	Leu Val Asn Gly Arg Gly Leu Asp Ser Thr Phe Gln Arg Arg Thr Gly 945	950	955
	Tyr Val Gln Gln Asp Val His Ile Gly Glu Ser Thr Val Arg Glu 965	970	975
30	Ala Leu Arg Phe Ser Ala Ala Leu Arg Gln Pro Ala Ser Val Pro Leu 980	985	990
	Ser Glu Lys Tyr Glu Tyr Val Glu Ser Val Ile Lys Leu Leu Glu Met 995	1000	1005
35	Glu Ser Tyr Ala Glu Ala Ile Ile Gly Thr Pro Gly Ser Gly Leu Asn 1010	1015	1020
	Val Glu Gln Arg Lys Arg Ala Thr Ile Gly Val Glu Leu Ala Ala Lys 1025	1030	1035
40	Pro Ala Leu Leu Phe Leu Asp Glu Pro Thr Ser Gly Leu Asp Ser 1045	1050	1055
	Gln Ser Ala Trp Ser Ile Val Cys Phe Leu Arg Lys Leu Ala Asp Ala 1060	1065	1070
45	Gly Gln Ala Ile Leu Cys Thr Ile His Gln Pro Ser Ala Val Leu Phe		
50			
55			

EP 1 217 066 A1

	1075	1080	1085
5	Asp Gln Phe Asp Arg Leu Leu Leu Gln Lys Gly Gly Lys Thr Val 1090	1095	1100
10	Tyr Phe Gly Asp Ile Gly Glu His Ser Lys Thr Leu Leu Asn Tyr Phe 1105	1110	1115
15	Glu Ser His Gly Ala Val His Cys Pro Asp Asp Gly Asn Pro Ala Glu 1125	1130	1135
20	Tyr Ile Leu Asp Val Ile Gly Ala Gly Ala Thr Ala Thr Thr Asn Arg 1140	1145	1150
25	Asp Trp His Glu Val Trp Asn Asn Ser Glu Glu Arg Lys Ala Ile Ser 1155	1160	1165
30	Ala Glu Leu Asp Lys Ile Asn Ala Ser Phe Ser Asn Ser Glu Asp Lys 1170	1175	1180
35	Lys Thr Leu Ser Lys Glu Asp Arg Ser Thr Tyr Ala Net Pro Leu Trp 1185	1190	1195
40	Phe Gln Val Lys Met Val Met Thr Arg Asn Phe Gln Ser Tyr Trp Arg 1205	1210	1215
45	Glu Pro Ser Ile Leu Met Ser Lys Leu Ala Leu Asp Ile Phe Ala Gly 1220	1225	1230
50	Leu Phe Ile Gly Phe Thr Phe Tyr Asn Gln Gly Leu Gly Val Gln Asn 1235	1240	1245
55	Ile Gln Asn Lys Leu Phe Ala Val Phe Met Ala Thr Val Leu Ala Val 1250	1255	1260
	Pro Leu Ile Asn Gly Leu Gln Pro Lys Phe Ile Glu Leu Arg Asn Val 1265	1270	1275
	Phe Glu Val Arg Glu Lys Pro Ser Asn Ile Tyr Ser Trp Val Ala Phe 1285	1290	1295
	Val Phe Ser Ala Ile Ile Val Glu Ile Pro Phe Asn Leu Val Phe Gly 1300	1305	1310
	Thr Leu Phe Phe Leu Cys Trp Phe Tyr Pro Ile Lys Phe Tyr Lys His 1315	1320	1325
	Ile His His Pro Gly Asp Lys Thr Gly Tyr Ala Trp Leu Leu Tyr Met		

EP 1 217 066 A1

	1330	1335	1340		
5	Phe Phe Gln Met Tyr Phe Ser Thr Phe Gly Gln Ala Val Ala Ser Ala 1345	1350	1355	1360	
	Cys Pro Asn Ala Gln Thr Ala Ser Val Val Asn Ser Leu Leu Phe Thr 1365	1370	1375		
10	Phe Val Ile Thr Phe Asn Gly Val Leu Gln Pro Asn Ser Asn Leu Val 1380	1385	1390		
	Gly Phe Trp His Trp Met His Ser Leu Thr Pro Phe Thr Tyr Leu Ile 1395	1400	1405		
15	Glu Gly Leu Leu Ser Asp Leu Val His Gly Leu Pro Val Glu Cys Lys 1410	1415	1420		
20	Ser His Glu Met Leu Thr Ile Asn Pro Pro Ser Gly Gln Thr Cys Gly 1425	1430	1435	1440	
	Glu Tyr Met Ser Ala Phe Leu Thr Asn Asn Thr Ala Ala Gly Asn Leu 1445	1450	1455		
25	Leu Asn Pro Asn Ala Thr Thr Ser Cys Ser Tyr Cys Pro Tyr Gln Thr 1460	1465	1470		
30	Ala Asp Gln Phe Leu Glu Arg Phe Ser Met Arg Tyr Thr His Arg Trp 1475	1480	1485		
	Arg Asn Leu Gly Ile Phe Val Gly Tyr Val Phe Phe Asn Ile Phe Ala 1490	1495	1500		
35	Val Leu Leu Leu Phe Tyr Val Phe Arg Val Met Lys Leu Arg Ser Thr 1505	1510	1515	1520	
	Trp Leu Gly Lys Lys Ile Thr Gly Thr Gly 1525	1530			
40	<210> 89 <211> 1501 <212> PRT <213> Candida albicans				
	<400> 89 Met Ser Asp Ser Lys Met Ser Ser Gln Asp Glu Ser Lys Leu Glu Lys 55	1	5	10	15

	Ala Ile Ser Gln Asp Ser Ser Ser Glu Asn His Ser Ile Asn Glu Tyr		
5	20	25	30
	His Gly Phe Asp Ala His Thr Ser Glu Asn Ile Gln Asn Leu Ala Arg		
	35	40	45
10	Thr Phe Thr His Asp Ser Phe Lys Asp Asp Ser Ser Ala Gly Leu Leu		
	50	55	60
15	Lys Tyr Leu Thr His Met Ser Glu Val Pro Gly Val Asn Pro Tyr Glu		
	65	70	75
	His Glu Glu Ile Asn Asn Asp Gln Leu Asn Pro Asp Ser Glu Asn Phe		
20	85	90	95
	Asn Ala Lys Phe Trp Val Lys Asn Leu Arg Lys Leu Phe Glu Ser Asp		
	100	105	110
25	Pro Glu Tyr Tyr Lys Pro Ser Lys Leu Gly Ile Gly Tyr Arg Asn Leu		
	115	120	125
	Arg Ala Tyr Gly Val Ala Asn Asp Ser Asp Tyr Gln Pro Thr Val Thr		
	130	135	140
30	Asn Ala Leu Trp Lys Leu Ala Thr Glu Gly Phe Arg His Phe Gln Lys		
	145	150	155
	160		
35	Asp Asp Asp Ser Arg Tyr Phe Asp Ile Leu Lys Ser Met Asp Ala Ile		
	165	170	175
	Met Arg Pro Gly Glu Leu Thr Val Val Leu Gly Arg Pro Gly Ala Gly		
	180	185	190
40	Cys Ser Thr Leu Leu Lys Thr Ile Ala Val Asn Thr Tyr Gly Phe His		
	195	200	205
45	Ile Gly Lys Glu Ser Gln Ile Thr Tyr Asp Gly Leu Ser Pro His Asp		
	210	215	220
	Ile Glu Arg His Tyr Arg Gly Asp Val Ile Tyr Ser Ala Glu Thr Asp		
50	225	230	235
	240		
	Val His Phe Pro His Leu Ser Val Gly Asp Thr Leu Glu Phe Ala Ala		
	245	250	255
55	Arg Leu Arg Thr Pro Gln Asn Arg Gly Glu Gly Ile Asp Arg Glu Thr		
	260	265	270

Tyr Ala Lys His Met Ala Ser Val Tyr Met Ala Thr Tyr Gly Leu Ser
 5 275 280 285

His Thr Arg Asn Thr Asn Val Gly Asn Asp Phe Val Arg Gly Val Ser
 10 290 295 300

Gly Gly Glu Arg Lys Arg Val Ser Ile Ala Glu Ala Ser Leu Ser Gly
 305 310 315 320

Ala Asn Ile Gln Cys Trp Asp Asn Ala Thr Arg Gly Leu Asp Ser Ala
 15 325 330 335

Thr Ala Leu Glu Phe Ile Arg Ala Leu Lys Thr Ser Ala Val Ile Leu
 340 345 350

20 Asp Thr Thr Pro Leu Ile Ala Ile Tyr Gln Cys Ser Gln Asp Ala Tyr
 355 360 365

Asp Leu Phe Asp Lys Val Val Val Leu Tyr Glu Gly Tyr Gln Ile Phe
 25 370 375 380

Phe Gly Lys Ala Thr Lys Ala Lys Glu Tyr Phe Glu Lys Met Gly Trp
 385 390 395 400

30 Lys Cys Pro Gln Arg Gln Thr Thr Ala Asp Phe Leu Thr Ser Leu Thr
 405 410 415

Asn Pro Ala Glu Arg Glu Pro Leu Pro Gly Tyr Glu Asp Lys Val Pro
 35 420 425 430

Arg Thr Ala Gln Glu Phe Glu Thr Tyr Trp Lys Asn Ser Pro Glu Tyr
 435 440 445

40 Ala Glu Leu Thr Lys Glu Ile Asp Glu Tyr Phe Val Glu Cys Glu Arg
 450 455 460

Ser Asn Thr Arg Glu Thr Tyr Arg Glu Ser His Val Ala Lys Gln Ser
 45 465 470 475 480

Asn Asn Thr Arg Pro Ala Ser Pro Tyr Thr Val Ser Phe Phe Met Gln
 485 490 495

50 Val Arg Tyr Gly Val Ala Arg Asn Phe Leu Arg Met Lys Gly Asp Pro
 500 505 510

Ser Ile Pro Ile Phe Ser Val Phe Gly Gln Leu Val Met Gly Leu Ile
 55 515 520 525

EP 1 217 066 A1

Leu Ser Ser Val Phe Tyr Asn Leu Ser Gln Thr Thr Gly Ser Phe Tyr
5 530 535 540

Tyr Arg Gly Ala Ala Met Phe Phe Ala Val Leu Phe Asn Ala Phe Ser
545 550 555 560

10 Ser Leu Leu Glu Ile Met Ser Leu Phe Glu Ala Arg Pro Ile Val Glu
565 570 575

Lys His Lys Lys Tyr Ala Leu Tyr Arg Pro Ser Ala Asp Ala Leu Ala
15 580 585 590

Ser Ile Ile Ser Glu Leu Pro Val Lys Leu Ala Met Ser Met Ser Phe
20 595 600 605

Asn Phe Val Phe Tyr Phe Met Val Asn Phe Arg Arg Asn Pro Gly Arg
610 615 620

Phe Phe Phe Tyr Trp Leu Met Cys Ile Trp Cys Thr Phe Val Met Ser
25 625 630 635 640

His Leu Phe Arg Ser Ile Gly Ala Val Ser Thr Ser Ile Ser Gly Ala
30 645 650 655

Met Thr Pro Ala Thr Val Leu Leu Ala Met Val Ile Tyr Thr Gly
660 665 670

Phe Val Ile Pro Thr Pro Ser Met Leu Gly Trp Ser Arg Trp Ile Asn
35 675 680 685

Tyr Ile Asn Pro Val Gly Tyr Val Phe Glu Ser Leu Met Val Asn Glu
40 690 695 700

Phe His Gly Arg Glu Phe Gln Cys Ala Gln Tyr Val Pro Ser Gly Pro
705 710 715 720

Gly Tyr Glu Asn Ile Ser Arg Ser Asn Gln Val Cys Thr Ala Val Gly
45 725 730 735

Ser Val Pro Gly Asn Glu Met Val Ser Gly Thr Asn Tyr Leu Ala Gly
50 740 745 750

Ala Tyr Gln Tyr Tyr Asn Ser His Lys Trp Arg Asn Leu Gly Ile Thr
755 760 765

Ile Gly Phe Ala Val Phe Phe Leu Ala Ile Tyr Ile Ala Leu Thr Glu
55 770 775 780

5 Phe Asn Lys Gly Ala Met Gln Lys Gly Glu Ile Val Leu Phe Leu Lys
 785 790 795 800

Gly Ser Leu Lys Lys His Lys Arg Lys Thr Ala Ala Ser Asn Lys Gly
 805 810 815

10 Asp Ile Glu Ala Gly Pro Val Ala Gly Lys Leu Asp Tyr Gln Asp Glu
 820 825 830

Ala Glu Ala Val Asn Asn Glu Lys Phe Thr Glu Lys Gly Ser Thr Gly
 15 835 840 845

Ser Val Asp Phe Pro Glu Asn Arg Glu Ile Phe Phe Trp Arg Asp Leu
 850 855 860

20 Thr Tyr Gln Val Lys Ile Lys Lys Glu Asp Arg Val Ile Leu Asp His
 865 870 875 880

Val Asp Gly Trp Val Lys Pro Gly Gln Ile Thr Ala Leu Met Gly Ala
 25 885 890 895

Ser Gly Ala Gly Lys Thr Thr Leu Leu Asn Cys Leu Ser Glu Arg Val
 900 905 910

30 Thr Thr Gly Ile Ile Thr Asp Gly Glu Arg Leu Val Asn Gly His Ala
 915 920 925

Leu Asp Ser Ser Phe Gln Arg Ser Ile Gly Tyr Val Gln Gln Gln Asp
 35 930 935 940

Val His Leu Pro Thr Ser Thr Val Arg Glu Ala Leu Gln Phe Ser Ala
 945 950 955 960

40 Tyr Leu Arg Gln Ser Asn Lys Ile Ser Lys Lys Glu Lys Asp Asp Tyr
 965 970 975

Val Asp Tyr Val Ile Asp Leu Leu Glu Met Thr Asp Tyr Ala Asp Ala
 45 980 985 990

Leu Val Gly Val Ala Gly Glu Gly Leu Asn Val Glu Gln Arg Lys Arg
 995 1000 1005

50 Leu Thr Ile Gly Val Glu Leu Val Ala Lys Pro Lys Leu Leu Leu Phe
 1010 1015 1020

Leu Asp Glu Pro Thr Ser Gly Leu Asp Ser Gln Thr Ala Trp Ser Ile
 55 1025 1030 1035 1040

EP 1 217 066 A1

Cys Lys Leu Met Arg Lys Leu Ala Asp His Gly Gln Ala Ile Leu Cys
5 1045 1050 1055

Thr Ile His Gln Pro Ser Ala Leu Ile Met Ala Glu Phe Asp Arg Leu
10 1060 1065 1070

Leu Phe Leu Gln Lys Gly Gly Arg Thr Ala Tyr Phe Gly Glu Leu Gly
15 1075 1080 1085

Glu Asn Cys Gln Thr Met Ile Asn Tyr Phe Glu Lys Tyr Gly Ala Asp
20 1090 1095 1100

Pro Cys Pro Lys Glu Ala Asn Pro Ala Glu Trp Met Leu Gln Val Val
25 1105 1110 1115 1120

Gly Ala Ala Pro Gly Ser His Ala Lys Gln Asp Tyr Phe Glu Val Trp
30 1125 1130 1135

Arg Asn Ser Ser Glu Tyr Gln Ala Val Arg Glu Glu Ile Asn Arg Met
35 1140 1145 1150

Glu Ala Glu Leu Ser Lys Leu Pro Arg Asp Asn Asp Pro Glu Ala Leu
40 1155 1160 1165

Leu Lys Tyr Ala Ala Pro Leu Trp Lys Gln Tyr Leu Leu Val Ser Trp
45 1170 1175 1180

Arg Thr Ile Val Gln Asp Trp Arg Ser Pro Gly Tyr Ile Tyr Ser Lys
50 1185 1190 1195 1200

Ile Phe Leu Val Val Ser Ala Ala Leu Phe Asn Gly Phe Ser Phe Phe
55 1205 1210 1215

Lys Ala Lys Asn Asn Met Gln Gly Leu Gln Asn Gln Met Phe Ser Val
1220 1225 1230

Phe Met Phe Phe Ile Pro Phe Asn Thr Leu Val Gln Gln Met Leu Pro
1235 1240 1245

Tyr Phe Val Lys Gln Arg Asp Val Tyr Glu Val Arg Glu Ala Pro Ser
1250 1255 1260

Arg Thr Phe Ser Trp Phe Ala Phe Ile Ala Gly Gln Ile Thr Ser Glu
1265 1270 1275 1280

Ile Pro Tyr Gln Val Ala Val Gly Thr Ile Ala Phe Phe Cys Trp Tyr
1285 1290 1295

Tyr Pro Leu Gly Leu Tyr Asn Asn Ala Thr Pro Thr Asp Ser Val Asn
 5 1300 1305 1310

Pro Arg Gly Val Leu Met Trp Met Leu Val Thr Ala Phe Tyr Val Tyr
 10 1315 1320 1325

Thr Ala Thr Met Gly Gln Leu Cys Met Ser Phe Ser Glu Leu Ala Asp
 1330 1335 1340

Asn Ala Ala Asn Leu Ala Thr Leu Leu Phe Thr Met Cys Leu Asn Phe
 15 1345 1350 1355 1360

Cys Gly Val Leu Ala Gly Pro Asp Val Leu Pro Gly Phe Trp Ile Phe
 1365 1370 1375

Met Tyr Arg Cys Asn Pro Phe Thr Tyr Leu Val Gln Ala Met Leu Ser
 20 1380 1385 1390

Thr Gly Leu Ala Asn Thr Phe Val Lys Cys Ala Glu Arg Glu Tyr Val
 25 1395 1400 1405

Ser Val Lys Pro Pro Asn Gly Glu Ser Cys Ser Thr Tyr Leu Asp Pro
 1410 1415 1420

Tyr Ile Lys Phe Ala Gly Gly Tyr Phe Glu Thr Arg Asn Asp Gly Ser
 30 1425 1430 1435 1440

Cys Ala Phe Cys Gln Met Ser Ser Thr Asn Thr Phe Leu Lys Ser Val
 35 1445 1450 1455

Asn Ser Leu Tyr Ser Glu Arg Trp Arg Asn Phe Gly Ile Phe Ile Ala
 1460 1465 1470

Phe Ile Ala Ile Asn Ile Ile Leu Thr Val Ile Phe Tyr Trp Leu Ala
 40 1475 1480 1485

Arg Val Pro Lys Gly Asn Arg Glu Lys Lys Asn Lys Lys
 45 1490 1495 1500

50 <210> 90
 <211> 1499
 <212> PRT
 <213> Candida albicans

55 <400> 90

EP 1 217 066 A1

Met Ser Thr Ala Asn Thr Ser Leu Ser Gln Gln Leu Asp Glu Asn Pro
1 5 10 15

5 Trp Val Asp Ala Ser Asp Asn Ser Ser Val Gln Glu Tyr Gln Gly Phe
20 25 30

10 Asp Ala Thr Ala Ser His Asn Ile Gln Asp Leu Ala Arg Lys Leu Thr
35 40 45

15 His Gly Ser Thr Asn Gly Asp His His Ser Ala Asn Asp Leu Ala Arg
50 55 60

20 Tyr Leu Ser His Met Ser Asp Ile Pro Gly Val Ser Pro Phe Asn Gly
65 70 75 80

25 Asn Ile Ser His Glu Gln Leu Asp Pro Asp Ser Glu Asn Phe Asn Ala
85 90 95

30 Lys Tyr Trp Val Lys Asn Leu Lys Lys Leu Phe Glu Ser Asp Ser Asp
100 105 110

35 Tyr Tyr Lys Pro Ser Lys Leu Gly Val Ala Tyr Arg Asn Leu Arg Ala
115 120 125

40 Tyr Gly Ile Ala Asn Asp Ser Asp Tyr Gln Pro Thr Val Thr Asn Ala
130 135 140

45 Leu Trp Lys Phe Thr Thr Glu Ala Ile Asn Lys Leu Lys Lys Pro Asp
145 150 155 160

50 Asp Ser Lys Tyr Phe Asp Ile Leu Lys Ser Met Asp Ala Ile Met Arg
165 170 175

55 Pro Gly Glu Leu Thr Val Val Leu Gly Arg Pro Gly Ala Gly Cys Ser
180 185 190

60 Thr Leu Leu Lys Thr Ile Ala Val Asn Thr Tyr Gly Phe His Ile Gly
195 200 205

65 Lys Glu Ser Gln Ile Thr Tyr Asp Gly Leu Ser Pro His Asp Ile Glu
210 215 220

70 Arg His Tyr Arg Gly Asp Val Ile Tyr Ser Ala Glu Thr Asp Val His
225 230 235 240

75 Phe Pro His Leu Ser Val Gly Asp Thr Leu Glu Phe Ala Ala Arg Leu
245 250 255

EP 1 217 066 A1

Arg Thr Pro Gln Asn Arg Gly Glu Gly Ile Asp Arg Glu Thr Tyr Ala
260 265 270

5 Lys His Met Ala Ser Val Tyr Met Ala Thr Tyr Gly Leu Ser His Thr
275 280 285

10 Arg Asn Thr Asn Val Gly Asn Asp Phe Val Arg Gly Val Ser Gly Gly
290 295 300

Glu Arg Lys Arg Val Ser Ile Ala Glu Ala Ser Leu Ser Gly Ala Asn
305 310 315 320

15 Ile Gln Cys Trp Asp Asn Ala Thr Arg Gly Leu Asp Ser Ala Thr Ala
325 330 335

20 Leu Glu Phe Ile Arg Ala Leu Lys Thr Ser Ala Thr Ile Leu Asp Thr
340 345 350

Thr Pro Leu Ile Ala Ile Tyr Gln Cys Ser Gln Asp Ala Tyr Glu Leu
355 360 365

25 Phe Asp Asn Val Val Leu Tyr Glu Gly Tyr Gln Ile Phe Phe Gly
370 375 380

30 Lys Ala Ser Lys Ala Lys Glu Tyr Phe Glu Asn Met Gly Trp Lys Cys
385 390 395 400

Pro Gln Arg Gln Thr Thr Ala Asp Phe Leu Thr Ser Leu Thr Asn Pro
405 410 415

35 Ala Glu Arg Glu Pro Leu Pro Gly Tyr Glu Asp Lys Val Pro Arg Thr
420 425 430

40 Ala Gln Glu Phe Glu Thr Phe Trp Lys Asn Ser Pro Glu Tyr Ala Glu
435 440 445

45 Leu Thr Lys Glu Ile Asp Glu Tyr Phe Val Glu Cys Glu Arg Ser Asn
450 455 460

Thr Gly Glu Thr Tyr Arg Glu Ser His Val Gly Lys Gln Ser Asn Asn
465 470 475 480

50 Thr Arg Pro Ser Ser Pro Tyr Thr Val Ser Phe Phe Met Gln Val Arg
485 490 495

Tyr Val Ile Ala Arg Asn Phe Leu Arg Met Lys Gly Asp Pro Ser Ile
55 500 505 510

EP 1 217 066 A1

Pro Leu Ile Ser Ile Leu Ser Gln Leu Val Met Gly Leu Ile Leu Ala
515 520 525

5 Ser Val Phe Phe Asn Leu Arg Lys Ser Thr Asp Thr Phe Tyr Phe Arg
530 535 540

10 Gly Gly Ala Leu Phe Phe Ser Val Leu Phe Asn Ala Phe Ser Ser Leu
545 550 555 560

Leu Glu Ile Leu Ser Leu Tyr Glu Ala Arg Pro Ile Val Glu Lys His
565 570 575

15 Arg Lys Tyr Ala Leu Tyr Arg Pro Ser Ala Asp Ala Leu Ala Ser Ile
580 585 590

20 Ile Ser Glu Leu Pro Val Lys Leu Leu Met Thr Met Ser Phe Asn Ile
595 600 605

Val Tyr Tyr Phe Met Val Asn Leu Arg Arg Thr Ala Gly Asn Phe Phe
610 615 620

25 Phe Tyr Trp Leu Met Cys Ala Ser Cys Thr Leu Val Met Ser His Met
625 630 635 640

30 Phe Arg Ser Ile Gly Ala Val Thr Thr Ile Ala Thr Ala Met Ser
645 650 655

Leu Ser Thr Val Phe Leu Leu Ala Met Ile Ile Tyr Ala Gly Phe Val
660 665 670

35 Leu Pro Ile Pro Tyr Ile Leu Gly Trp Ser Arg Trp Ile Arg Tyr Ile
675 680 685

40 Asn Pro Val Thr Tyr Ile Phe Glu Ser Leu Met Val Asn Glu Phe His
690 695 700

45 Gly Arg Glu Phe Glu Cys Gly Gln Tyr Ile Pro Ser Gly Pro Gly Phe
705 710 715 720

Glu Asn Leu Pro Val Glu Asn Lys Val Cys Thr Thr Val Gly Ser Thr
725 730 735

50 Pro Gly Ser Thr Val Val Gln Gly Thr Glu Tyr Ile Lys Leu Ala Tyr
740 745 750

55 Gln Phe Tyr Ser Ser His Lys Trp Arg Asn Phe Gly Ile Thr Val Ala
755 760 765

EP 1 217 066 A1

Phe Ala Val Phe Phe Leu Gly Val Tyr Val Ala Leu Thr Glu Phe Asn
770 775 780

5 Lys Gly Ala Ser Gln Lys Gly Glu Ile Val Leu Phe Leu Lys Gly Ser
785 790 795 800

Leu Lys Lys His Lys Arg Lys Thr Ala Ala Ser Asn Lys Gly Asp Ile
10 805 810 815

Glu Ala Gly Pro Val Ala Gly Lys Leu Asp Tyr Gln Asp Glu Ala Glu
820 825 830

15 Ala Val Asn Asn Glu Lys Phe Thr Glu Lys Gly Ser Thr Gly Ser Val
835 840 845

Asp Phe Pro Glu Asn Arg Glu Ile Phe Phe Trp Arg Asp Leu Thr Tyr
20 850 855 860

Gln Val Lys Ile Lys Lys Glu Asp Arg Val Ile Leu Asp His Val Asp
865 870 875 880

25 Gly Trp Val Lys Pro Gly Gln Ile Thr Ala Leu Met Gly Ala Ser Gly
885 890 895

Ala Gly Lys Thr Thr Leu Leu Asn Cys Leu Ser Glu Arg Val Thr Thr
30 900 905 910

Gly Ile Ile Thr Asp Gly Glu Arg Leu Val Asn Gly His Ala Leu Asp
915 920 925

35 Ser Ser Phe Gln Arg Ser Ile Gly Tyr Val Gln Gln Gln Asp Val His
930 935 940

Leu Glu Thr Thr Thr Val Arg Glu Ala Leu Gln Phe Ser Ala Tyr Leu
40 945 950 955 960

Arg Gln Ser Asn Lys Ile Ser Lys Lys Glu Lys Asp Asp Tyr Val Asp
45 965 970 975

Tyr Val Ile Asp Leu Leu Glu Met Thr Asp Tyr Ala Asp Ala Leu Val
980 985 990

50 Gly Val Ala Gly Glu Gly Leu Asn Val Glu Gln Arg Lys Arg Leu Thr
995 1000 1005

Ile Gly Val Glu Leu Val Ala Lys Pro Lys Leu Leu Leu Phe Leu Asp
55 1010 1015 1020

EP 1 217 066 A1

Glu Pro Thr Ser Gly Leu Asp Ser Gln Thr Ala Trp Ser Ile Cys Lys
1025 1030 1035 1040

5 Leu Met Arg Lys Leu Ala Asp His Gly Gln Ala Ile Leu Cys Thr Ile
1045 1050 1055

10 His Gln Pro Ser Ala Leu Ile Met Ala Glu Phe Asp Lys Leu Leu Phe
1060 1065 1070

15 Leu Gln Lys Gly Gly Arg Thr Ala Tyr Phe Gly Glu Leu Gly Glu Asn
1075 1080 1085

20 Cys Gln Thr Met Ile Asn Tyr Phe Glu Lys Tyr Gly Ala Asp Pro Cys
1090 1095 1100

25 Pro Lys Glu Ala Asn Pro Ala Glu Trp Met Leu Gln Val Val Gly Ala
1105 1110 1115 1120

30 Ala Pro Gly Ser His Ala Lys Gln Asp Tyr Phe Glu Val Trp Arg Asn
1125 1130 1135

25 Ser Ser Glu Tyr Gln Ala Val Arg Glu Glu Ile Asn Arg Met Glu Ala
1140 1145 1150

35 Glu Leu Ser Lys Leu Pro Arg Asp Asn Asp Pro Glu Ala Leu Leu Lys
1155 1160 1165

35 Tyr Ala Ala Pro Leu Trp Lys Gln Tyr Leu Leu Val Ser Trp Arg Thr
1170 1175 1180

40 Ile Val Gln Asp Trp Arg Ser Pro Gly Tyr Ile Tyr Ser Lys Leu Ile
1185 1190 1195 1200

45 Leu Val Ile Ser Ser Ser Leu Phe Ile Gly Phe Ser Phe Phe Lys Ser
1205 1210 1215

45 Lys Asn Asn Leu Gln Gly Leu Gln Ser Gln Met Leu Ala Val Phe Met
1220 1225 1230

50 Phe Phe Val Pro Phe Thr Thr Phe Ile Asp Gln Met Leu Pro Tyr Phe
1235 1240 1245

55 Val Lys His Arg Ala Val Tyr Glu Val Arg Glu Ala Pro Ser Arg Thr
1250 1255 1260

55 Phe Ser Trp Phe Ala Phe Ile Ala Gly Gln Ile Thr Ser Glu Ile Pro
1265 1270 1275 1280

EP 1 217 066 A1

Phe Gln Ile Val Val Gly Thr Ile Ser Tyr Phe Cys Trp Tyr Tyr Pro
1285 1290 1295

5 Val Gly Leu Tyr Ala Asn Ala Glu Pro Thr Asp Ser Val Asn Ser Arg
1300 1305 1310

Gly Val Leu Met Trp Met Leu Leu Thr Ala Phe Tyr Val Tyr Thr Ser
10 1315 1320 1325

Thr Met Gly Gln Leu Ala Ile Ser Leu Asn Glu Leu Ile Asp Asn Ala
1330 1335 1340

15 Ala Asn Leu Ala Thr Thr Leu Phe Thr Leu Cys Leu Met Phe Cys Gly
1345 1350 1355 1360

Val Leu Ala Gly Pro Asn Val Ile Pro Gly Phe Trp Ile Phe Met Tyr
20 1365 1370 1375

Arg Cys Asn Pro Phe Thr Tyr Leu Ile Gln Ala Ile Leu Ser Thr Gly
1380 1385 1390

25 Leu Ala Asn Ala Lys Val Thr Cys Ala Pro Arg Glu Leu Val Thr Leu
1395 1400 1405

Lys Pro Pro Met Gly Glu Thr Cys Ser Ser Phe Ile Gly Pro Tyr Thr
30 1410 1415 1420

Glu Ala Ala Gly Gly Tyr Phe Ser Thr Asn Ser Asp Gly Thr Cys Ser
1425 1430 1435 1440

35 Val Cys Arg Ile Asp Ser Thr Asn Gln Phe Leu Glu Ser Ile Asn Ala
1445 1450 1455

Leu Phe Ser Gln Arg Trp Arg Asn Phe Gly Ile Phe Val Ala Phe Ile
40 1460 1465 1470

Gly Ile Asn Ile Ile Leu Thr Ile Phe Phe Tyr Trp Leu Ala Arg Val
45 1475 1480 1485

Pro Lys Gly Asn Arg Glu Lys Lys Met Lys Lys
1490 1495

50

<210> 91
<211> 1511
55 <212> PRT
<213> *Saccharomyces cerevisiae*

<400> 91

5	Met Pro Glu Ala Lys Leu Asn Asn Asn Val Asn Asp Val Thr Ser Tyr			
	1	5	10	15
	Ser Ser Ala Ser Ser Ser Thr Glu Asn Ala Ala Asp Leu His Asn Tyr			
10	20	25	30	
	Asn Gly Phe Asp Glu His Thr Glu Ala Arg Ile Gln Lys Leu Ala Arg			
	35	40	45	
15	Thr Leu Thr Ala Gln Ser Met Gln Asn Ser Thr Gln Ser Ala Pro Asn			
	50	55	60	
20	Lys Ser Asp Ala Gln Ser Ile Phe Ser Ser Gly Val Glu Gly Val Asn			
	65	70	75	80
	Pro Ile Phe Ser Asp Pro Glu Ala Pro Gly Tyr Asp Pro Lys Leu Asp			
	85	90	95	
25	Pro Asn Ser Glu Asn Phe Ser Ser Ala Ala Trp Val Lys Asn Met Ala			
	100	105	110	
30	His Leu Ser Ala Ala Asp Pro Asp Phe Tyr Lys Pro Tyr Ser Leu Gly			
	115	120	125	
	Cys Ala Trp Lys Asn Leu Ser Ala Ser Gly Ala Ser Ala Asp Val Ala			
	130	135	140	
35	Tyr Gln Ser Thr Val Val Asn Ile Pro Tyr Lys Ile Leu Lys Ser Gly			
	145	150	155	160
40	Leu Arg Lys Phe Gln Arg Ser Lys Glu Thr Asn Thr Phe Gln Ile Leu			
	165	170	175	
	Lys Pro Met Asp Gly Cys Leu Asn Pro Gly Glu Leu Leu Val Val Leu			
	180	185	190	
45	Gly Arg Pro Gly Ser Gly Cys Thr Thr Leu Leu Lys Ser Ile Ser Ser			
	195	200	205	
50	Asn Thr His Gly Phe Asp Leu Gly Ala Asp Thr Lys Ile Ser Tyr Ser			
	210	215	220	
	Gly Tyr Ser Gly Asp Asp Ile Lys Lys His Phe Arg Gly Glu Val Val			
	225	230	235	240
55	Tyr Asn Ala Glu Ala Asp Val His Leu Pro His Leu Thr Val Phe Glu			

	245	250	255
5	Thr Leu Val Thr Val Ala Arg Leu Lys Thr Pro Gln Asn Arg Ile Lys 260	265	270
10	Gly Val Asp Arg Glu Ser Tyr Ala Asn His Leu Ala Glu Val Ala Met 275	280	285
15	Ala Thr Tyr Gly Leu Ser His Thr Arg Asn Thr Lys Val Gly Asn Asp 290	295	300
20	Ile Val Arg Gly Val Ser Gly Gly Glu Arg Lys Arg Val Ser Ile Ala 305	310	315
	Glu Val Ser Ile Cys Gly Ser Lys Phe Gln Cys Trp Asp Asn Ala Thr 325	330	335
	Arg Gly Leu Asp Ser Ala Thr Ala Leu Glu Phe Ile Arg Ala Leu Lys 340	345	350
25	Thr Gln Ala Asp Ile Ser Asn Thr Ser Ala Thr Val Ala Ile Tyr Gln 355	360	365
30	Cys Ser Gln Asp Ala Tyr Asp Leu Phe Asn Lys Val Cys Val Leu Asp 370	375	380
	Asp Gly Tyr Gln Ile Tyr Tyr Gly Pro Ala Asp Lys Ala Lys Lys Tyr 385	390	395
35	Phe Glu Asp Met Gly Tyr Val Cys Pro Ser Arg Gln Thr Thr Ala Asp 405	410	415
40	Phe Leu Thr Ser Val Thr Ser Pro Ser Glu Arg Thr Leu Asn Lys Asp 420	425	430
	Met Leu Lys Lys Gly Ile His Ile Pro Gln Thr Pro Lys Glu Met Asn 435	440	445
45	Asp Tyr Trp Val Lys Ser Pro Asn Tyr Lys Glu Leu Met Lys Glu Val 450	455	460
50	Asp Gln Arg Leu Leu Asn Asp Asp Glu Ala Ser Arg Glu Ala Ile Lys 465	470	475
	Glu Ala His Ile Ala Lys Gln Ser Lys Arg Ala Arg Pro Ser Ser Pro 485	490	495
55	Tyr Thr Val Ser Tyr Met Met Gln Val Lys Tyr Leu Leu Ile Arg Asn		

EP 1 217 066 A1

	500	505	510
5	Met Trp Arg Leu Arg Asn Asn Ile Gly Phe Thr Leu Phe Met Ile Leu 515	520	525
10	Gly Asn Cys Ser Met Ala Leu Ile Leu Gly Ser Met Phe Phe Lys Ile 530	535	540
15	Met Lys Lys Gly Asp Thr Ser Thr Phe Tyr Phe Arg Gly Ser Ala Met 545	550	555
20	Phe Phe Ala Ile Leu Phe Asn Ala Phe Ser Ser Leu Leu Glu Ile Phe 565	570	575
25	Ser Leu Tyr Glu Ala Arg Pro Ile Thr Glu Lys His Arg Thr Tyr Ser 580	585	590
30	Leu Tyr His Pro Ser Ala Asp Ala Phe Ala Ser Val Leu Ser Glu Ile 595	600	605
35	Pro Ser Lys Leu Ile Ile Ala Val Cys Phe Asn Ile Ile Phe Tyr Phe 610	615	620
40	Leu Val Asp Phe Arg Arg Asn Gly Gly Val Phe Phe Tyr Leu Leu 625	630	635
45	Ile Asn Ile Val Ala Val Phe Ser Met Ser His Leu Phe Arg Cys Val 645	650	655
50	Gly Ser Leu Thr Lys Thr Leu Ser Glu Ala Met Val Pro Ala Ser Met 660	665	670
55	Leu Leu Leu Ala Leu Ser Met Tyr Thr Gly Phe Ala Ile Pro Lys Lys 675	680	685
	Lys Ile Leu Arg Trp Ser Lys Trp Ile Trp Tyr Ile Asn Pro Leu Ala 690	695	700
	Tyr Leu Phe Glu Ser Leu Leu Ile Asn Glu Phe His Gly Ile Lys Phe 705	710	715
	Pro Cys Ala Glu Tyr Val Pro Arg Gly Pro Ala Tyr Ala Asn Ile Ser 725	730	735
	Ser Thr Glu Ser Val Cys Thr Val Val Gly Ala Val Pro Gly Gln Asp 740	745	750
	Tyr Val Leu Gly Asp Asp Phe Ile Arg Gly Thr Tyr Gln Tyr Tyr His		

EP 1 217 066 A1

	755	760	765
5	Lys Asp Lys Trp Arg Gly Phe Gly Ile Gly Met Ala Tyr Val Val Phe 770	775	780
10	Phe Phe Phe Val Tyr Leu Phe Leu Cys Glu Tyr Asn Glu Gly Ala Lys 785	790	795
15	Gln Lys Gly Glu Ile Leu Val Phe Pro Arg Ser Ile Val Lys Arg Met 805	810	815
20	Lys Lys Arg Gly Val Leu Thr Glu Lys Asn Ala Asn Asp Pro Glu Asn 820	825	830
25	Val Gly Glu Arg Ser Asp Leu Ser Ser Asp Arg Lys Met Leu Gln Glu 835	840	845
30	Ser Ser Glu Glu Glu Ser Asp Thr Tyr Gly Glu Ile Gly Leu Ser Lys 850	855	860
35	Ser Glu Ala Ile Phe His Trp Arg Asn Leu Cys Tyr Glu Val Gln Ile 865	870	875
40	Lys Ala Glu Thr Arg Arg Ile Leu Asn Asn Val Asp Gly Trp Val Lys 885	890	895
45	Pro Gly Thr Leu Thr Ala Leu Met Gly Ala Ser Gly Ala Gly Lys Thr 900	905	910
50	Thr Leu Leu Asp Cys Leu Ala Glu Arg Val Thr Met Gly Val Ile Thr 915	920	925
55	Gly Asp Ile Leu Val Asn Gly Ile Pro Arg Asp Lys Ser Phe Pro Arg 930	935	940
60	Ser Ile Gly Tyr Cys Gln Gln Asp Leu His Leu Lys Thr Ala Thr 945	950	955
65	Val Arg Glu Ser Leu Arg Phe Ser Ala Tyr Leu Arg Gln Pro Ala Glu 965	970	975
70	Val Ser Ile Glu Glu Lys Asn Arg Tyr Val Glu Val Ile Lys Ile 980	985	990
75	Leu Glu Met Glu Lys Tyr Ala Asp Ala Val Val Gly Val Ala Gly Glu 995	1000	1005
80	Gly Leu Asn Val Glu Gln Arg Lys Arg Leu Thr Ile Gly Val Glu Leu		

EP 1 217 066 A1

	1010	1015	1020	
5	Thr Ala Lys Pro Lys Leu Leu Val Phe Leu Asp Glu Pro Thr Ser Gly 1025	1030	1035	1040
	Leu Asp Ser Gln Thr Ala Trp Ser Ile Cys Gln Leu Met Lys Lys Leu 1045	1050		1055
10	Ala Asn His Gly Gln Ala Ile Leu Cys Thr Ile His Gln Pro Ser Ala 1060	1065		1070
15	Ile Leu Met Gln Glu Phe Asp Arg Leu Leu Phe Met Gln Arg Gly Gly 1075	1080		1085
	Lys Thr Val Tyr Phe Gly Asp Leu Gly Glu Gly Cys Lys Thr Met Ile 1090	1095		1100
20	Asp Tyr Phe Glu Ser His Gly Ala His Lys Cys Pro Ala Asp Ala Asn 1105	1110	1115	1120
25	Pro Ala Glu Trp Met Leu Glu Val Val Gly Ala Ala Pro Gly Ser His 1125	1130		1135
	Ala Asn Gln Asp Tyr Tyr Glu Val Trp Arg Asn Ser Glu Glu Tyr Arg 1140	1145		1150
30	Ala Val Gln Ser Glu Leu Asp Trp Met Glu Arg Glu Leu Pro Lys Lys 1155	1160		1165
35	Gly Ser Ile Thr Ala Ala Glu Asp Lys His Glu Phe Ser Gln Ser Ile 1170	1175		1180
	Ile Tyr Gln Thr Lys Leu Val Ser Ile Arg Leu Phe Gln Gln Tyr Trp 1185	1190	1195	1200
40	Arg Ser Pro Asp Tyr Leu Trp Ser Lys Phe Ile Leu Thr Ile Phe Asn 1205	1210		1215
45	Gln Leu Phe Ile Gly Phe Thr Phe Phe Lys Ala Gly Thr Ser Leu Gln 1220	1225		1230
	Gly Leu Gln Asn Gln Met Leu Ala Val Phe Met Phe Thr Val Ile Phe 1235	1240		1245
50	Asn Pro Ile Leu Gln Gln Tyr Leu Pro Ser Phe Val Gln Gln Arg Asp 1250	1255		1260
55	Leu Tyr Glu Ala Arg Glu Arg Pro Ser Arg Thr Phe Ser Trp Ile Ser			

EP 1 217 066 A1

	1265	1270	1275	1280
5	Phe Ile Phe Ala Gln Ile Phe Val Glu Val Pro Trp Asn Ile Leu Ala			
	1285		1290	1295
	Gly Thr Ile Ala Tyr Phe Ile Tyr Tyr Tyr Pro Ile Gly Phe Tyr Ser			
10	1300		1305	1310
	Asn Ala Ser Ala Ala Gly Gln Leu His Glu Arg Gly Ala Leu Phe Trp			
	1315		1320	1325
15	Leu Phe Ser Cys Ala Phe Tyr Val Tyr Val Gly Ser Met Gly Leu Leu			
	1330		1335	1340
	Val Ile Ser Phe Asn Gln Val Ala Glu Ser Ala Ala Asn Leu Ala Ser			
20	1345		1350	1355
	Leu Leu Phe Thr Met Ser Leu Ser Phe Cys Gly Val Met Thr Thr Pro			
	1365		1370	1375
25	Ser Ala Met Pro Arg Phe Trp Ile Phe Met Tyr Arg Val Ser Pro Leu			
	1380		1385	1390
	Thr Tyr Phe Ile Gln Ala Leu Leu Ala Val Gly Val Ala Asn Val Asp			
30	1395		1400	1405
	Val Lys Cys Ala Asp Tyr Glu Leu Leu Glu Phe Thr Pro Pro Ser Gly			
	1410		1415	1420
35	Met Thr Cys Gly Gln Tyr Met Glu Pro Tyr Leu Gln Leu Ala Lys Thr			
	1425		1430	1435
	Gly Tyr Leu Thr Asp Glu Asn Ala Thr Asp Thr Cys Ser Phe Cys Gln			
40	1445		1450	1455
	Ile Ser Thr Thr Asn Asp Tyr Leu Ala Asn Val Asn Ser Phe Tyr Ser			
	1460		1465	1470
45	Glu Arg Trp Arg Asn Tyr Gly Ile Phe Ile Cys Tyr Ile Ala Phe Asn			
	1475		1480	1485
	Tyr Ile Ala Gly Val Phe Phe Tyr Trp Leu Ala Arg Val Pro Lys Lys			
50	1490		1495	1500
	Asn Gly Lys Leu Ser Lys Lys			
	1505		1510	

55

5 <210> 92
 <211> 1501
 <212> PRT
 <213> *Saccharomyces cerevisiae*

10 <400> 92
 Met Ser Asn Ile Lys Ser Thr Gln Asp Ser Ser His Asn Ala Val Ala
 1 5 10 15

15 Arg Ser Ser Ser Ala Ser Phe Ala Ala Ser Glu Glu Ser Phe Thr Gly
 . 20 25 30

20 Ile Thr His Asp Lys Asp Glu Gln Ser Asp Thr Pro Ala Asp Lys Leu
 . 35 40 45

25 Thr Lys Met Leu Thr Gly Pro Ala Arg Asp Thr Ala Ser Gln Ile Ser
 . 50 55 60

30 Ala Thr Val Ser Glu Met Ala Pro Asp Val Val Ser Lys Val Glu Ser
 . 65 70 75 80

35 Phe Ala Asp Ala Leu Ser Arg His Thr Thr Arg Ser Gly Ala Phe Asn
 . 85 90 95

40 Met Asp Ser Asp Ser Asp Asp Gly Phe Asp Ala His Ala Ile Phe Glu
 . 100 105 110

45 Ser Phe Val Arg Asp Ala Asp Glu Gln Gly Ile His Ile Arg Lys Ala
 . 115 120 125

50 Gly Val Thr Ile Glu Asp Val Ser Ala Lys Gly Val Asp Ala Ser Ala
 . 130 135 140

55 Leu Glu Gly Ala Thr Phe Gly Asn Ile Leu Cys Leu Pro Leu Thr Ile
 . 145 150 155 160

60 Phe Lys Gly Ile Lys Ala Lys Arg His Gln Lys Met Arg Gln Ile Ile
 . 165 170 175

65 Ser Asn Val Asn Ala Leu Ala Glu Ala Gly Glu Met Ile Leu Val Leu
 . 180 185 190

70 Gly Arg Pro Gly Ala Gly Cys Ser Ser Phe Leu Lys Val Thr Ala Gly
 . 195 200 205

75 Glu Ile Asp Gln Phe Ala Gly Gly Val Ser Gly Glu Val Ala Tyr Asp
 . 210 215 220

EP 1 217 066 A1

Gly Ile Pro Gln Glu Met Met Lys Arg Tyr Lys Ala Asp Val Ile
 225 230 235 240
 5
 Tyr Asn Gly Glu Leu Asp Val His Phe Pro Tyr Leu Thr Val Lys Gln
 245 250 255
 10
 Thr Leu Asp Phe Ala Ile Ala Cys Lys Thr Pro Ala Leu Arg Val Asn
 260 265 270
 15
 Asn Val Ser Lys Lys Glu Tyr Ile Ala Ser Arg Arg Asp Leu Tyr Ala
 275 280 285
 20
 Thr Ile Phe Gly Leu Arg His Thr Tyr Asn Thr Lys Val Gly Asn Asp
 290 295 300
 25
 Phe Val Arg Gly Val Ser Gly Gly Glu Arg Lys Arg Val Ser Ile Ala
 305 310 315 320
 Glu Ala Leu Ala Ala Lys Gly Ser Ile Tyr Cys Trp Asp Asn Ala Thr
 325 330 335
 30
 Arg Gly Leu Asp Ala Ser Thr Ala Leu Glu Tyr Ala Lys Ala Ile Arg
 340 345 350
 35
 Ile Met Thr Asn Leu Leu Lys Ser Thr Ala Phe Val Thr Ile Tyr Gln
 355 360 365
 Ala Ser Glu Asn Ile Tyr Glu Thr Phe Asp Lys Val Thr Val Leu Tyr
 370 375 380
 40
 Ser Gly Lys Gln Ile Tyr Phe Gly Leu Ile His Glu Ala Lys Pro Tyr
 385 390 395 400
 Phe Ala Lys Met Gly Tyr Leu Cys Pro Pro Arg Gln Ala Thr Ala Glu
 405 410 415
 45
 Phe Leu Thr Ala Leu Thr Asp Pro Asn Gly Phe His Leu Ile Lys Pro
 420 425 430
 50
 Gly Tyr Glu Asn Lys Val Pro Arg Thr Ala Glu Glu Phe Glu Thr Tyr
 435 440 445
 Trp Leu Asn Ser Pro Glu Phe Ala Gln Met Lys Lys Asp Ile Ala Ala
 450 455 460
 55
 Tyr Lys Glu Lys Val Asn Thr Glu Lys Thr Lys Glu Val Tyr Asp Glu
 465 470 475 480

EP 1 217 066 A1

Ser Met Ala Gln Glu Lys Ser Lys Tyr Thr Arg Lys Lys Ser Tyr Tyr
485 490 495

5 Thr Val Ser Tyr Trp Glu Gln Val Lys Leu Cys Thr Gln Arg Gly Phe
500 505 510

10 Gln Arg Ile Tyr Gly Asn Lys Ser Tyr Thr Val Ile Asn Val Cys Ser
515 520 525

15 Ala Ile Ile Gln Ser Phe Ile Thr Gly Ser Leu Phe Tyr Asn Thr Pro
530 535 540

20 Ser Ser Thr Ser Gly Ala Phe Ser Arg Gly Gly Val Leu Tyr Phe Ala
545 550 555 560

25 Leu Leu Tyr Tyr Ser Leu Met Gly Leu Ala Asn Ile Ser Phe Glu His
565 570 575

Arg Pro Ile Leu Gln Lys His Lys Gly Tyr Ser Leu Tyr His Pro Ser
580 585 590

30 Ala Glu Ala Ile Gly Ser Thr Leu Ala Ser Phe Pro Phe Arg Met Ile
595 600 605

35 Gly Leu Thr Cys Phe Phe Ile Ile Leu Phe Phe Leu Ser Gly Leu His
610 615 620

40 Arg Thr Ala Gly Ser Phe Phe Thr Ile Tyr Leu Phe Leu Thr Met Cys
625 630 635 640

45 Ser Glu Ala Ile Asn Gly Leu Phe Glu Met Val Ser Ser Val Cys Asp
645 650 655

50 Thr Leu Ser Gln Ala Asn Ser Ile Ser Gly Ile Leu Met Met Ser Ile
660 665 670

55 Ser Met Tyr Ser Thr Tyr Met Ile Gln Leu Pro Ser Met His Pro Trp
675 680 685

Phe Lys Trp Ile Ser Tyr Val Leu Pro Ile Arg Tyr Ala Phe Glu Ser
690 695 700

Met Leu Asn Ala Glu Phe His Gly Arg His Met Asp Cys Ala Asn Thr
705 710 715 720

Leu Val Pro Ser Gly Gly Asp Tyr Asp Asn Leu Ser Asp Asp Tyr Lys
725 730 735

EP 1 217 066 A1

Val Cys Ala Phe Val Gly Ser Lys Pro Gly Gln Ser Tyr Val Leu Gly
740 745 750

5 Asp Asp Tyr Leu Lys Asn Gln Phe Gln Tyr Val Tyr Lys His Thr Trp
755 760 765

10 Arg Asn Phe Gly Ile Leu Trp Cys Phe Leu Leu Gly Tyr Val Val Leu
770 775 780

Lys Val Ile Phe Thr Glu Tyr Lys Arg Pro Val Lys Gly Gly Asp
785 790 795 800

15 Ala Leu Ile Phe Lys Lys Gly Ser Lys Arg Phe Ile Ala His Ala Asp
805 810 815

20 Glu Glu Ser Pro Asp Asn Val Asn Asp Ile Asp Ala Lys Glu Gln Phe
820 825 830

Ser Ser Glu Ser Ser Gly Ala Asn Asp Glu Val Phe Asp Asp Leu Glu
25 835 840 845

Ala Lys Gly Val Phe Ile Trp Lys Asp Val Cys Phe Thr Ile Pro Tyr
850 855 860

30 Glu Gly Gly Lys Arg Met Leu Leu Asp Asn Val Ser Gly Tyr Cys Ile
865 870 875 880

Pro Gly Thr Met Thr Ala Leu Met Gly Glu Ser Gly Ala Gly Lys Thr
35 885 890 895

Thr Leu Leu Asn Thr Leu Ala Gln Arg Asn Val Gly Ile Ile Thr Gly
900 905 910

40 Asp Met Leu Val Asn Gly Arg Pro Ile Asp Ala Ser Phe Glu Arg Arg
915 920 925

45 Thr Gly Tyr Val Gln Gln Asp Ile His Ile Ala Glu Leu Thr Val
930 935 940

Arg Glu Ser Leu Gln Phe Ser Ala Arg Met Arg Arg Pro Gln His Leu
945 950 955 960

50 Pro Asp Ser Glu Lys Met Asp Tyr Val Glu Lys Ile Ile Arg Val Leu
965 970 975

55 Gly Met Glu Glu Tyr Ala Glu Ala Leu Val Gly Glu Val Gly Cys Gly
980 985 990

EP 1 217 066 A1

Leu Asn Val Glu Gln Arg Lys Lys Leu Ser Ile Gly Val Glu Leu Val
 995 1000 1005
 5 Ala Lys Pro Asp Leu Leu Leu Phe Leu Asp Glu Pro Thr Ser Gly Leu
 1010 1015 1020
 10 Asp Ser Gln Ser Ser Trp Ala Ile Ile Gln Leu Leu Arg Lys Leu Ser
 1025 1030 1035 1040
 15 Lys Ala Gly Gln Ser Ile Leu Cys Thr Ile His Gln Pro Ser Ala Thr
 1045 1050 1055
 15 Leu Phe Glu Glu Phe Asp Arg Leu Leu Leu Leu Arg Lys Gly Gly Gln
 1060 1065 1070
 20 Thr Val Tyr Phe Gly Asp Ile Gly Lys Asn Ser Ala Thr Ile Leu Asn
 1075 1080 1085
 25 Tyr Phe Glu Arg Asn Gln Ala Arg Lys Cys Asp Ser Ser Glu Asn Pro
 1090 1095 1100
 25 Ala Glu Tyr Ile Leu Glu Ala Ile Gly Ala Gly Ala Thr Ala Ser Val
 1105 1110 1115 1120
 30 Lys Glu Asp Trp His Glu Lys Trp Leu Asn Ser Val Glu Phe Glu Gln
 1125 1130 1135
 35 Thr Lys Glu Lys Val Gln Asp Leu Ile Asn Asp Leu Ser Lys Gln Glu
 1140 1145 1150
 35 Thr Lys Ser Glu Val Gly Asp Lys Pro Ser Lys Tyr Ala Thr Ser Tyr
 1155 1160 1165
 40 Ala Tyr Gln Phe Arg Tyr Val Leu Ile Arg Thr Ser Thr Ser Phe Trp
 1170 1175 1180
 45 Arg Ser Leu Asn Tyr Ile Met Ser Lys Met Met Leu Met Leu Val Gly
 1185 1190 1195 1200
 50 Gly Leu Tyr Ile Gly Phe Thr Phe Phe Asn Val Gly Lys Ser Tyr Val
 1205 1210 1215
 50 Gly Leu Gln Asn Ala Met Phe Ala Ala Phe Ile Ser Ile Ile Leu Ser
 1220 1225 1230
 55 Ala Pro Ala Met Asn Gln Ile Gln Gly Arg Ala Ile Ala Ser Arg Glu
 1235 1240 1245

EP 1 217 066 A1

Leu Phe Glu Val Arg Glu Ser Gln Ser Asn Met Phe His Trp Ser Leu
1250 1255 1260

5 Val Leu Ile Thr Gln Tyr Leu Ser Glu Leu Pro Tyr His Leu Phe Phe
1265 1270 1275 1280

10 Ser Thr Ile Phe Phe Val Ser Ser Tyr Phe Pro Leu Arg Ile Phe Phe
1285 1290 1295

Glu Ala Ser Arg Ser Ala Val Tyr Phe Leu Asn Tyr Cys Ile Met Phe
15 1300 1305 1310

Gln Leu Tyr Tyr Val Gly Leu Gly Leu Met Ile Leu Tyr Met Ser Pro
1315 1320 1325

20 Asn Leu Pro Ser Ala Asn Val Ile Leu Gly Leu Cys Leu Ser Phe Met
1330 1335 1340

Leu Ser Phe Cys Gly Val Thr Gln Pro Val Ser Leu Met Pro Gly Phe
25 1345 1350 1355 1360

Trp Thr Phe Met Trp Lys Ala Ser Pro Tyr Thr Tyr Phe Val Gln Asn
1365 1370 1375

30 Leu Val Gly Ile Met Leu His Lys Lys Pro Val Val Cys Lys Lys Lys
1380 1385 1390

Glu Leu Asn Tyr Phe Asn Pro Pro Asn Gly Ser Thr Cys Gly Glu Tyr
35 1395 1400 1405

Met Lys Pro Phe Leu Glu Lys Ala Thr Gly Tyr Ile Glu Asn Pro Asp
1410 1415 1420

40 Ala Thr Ser Asp Cys Ala Tyr Cys Ile Tyr Glu Val Gly Asp Asn Tyr
1425 1430 1435 1440

Leu Thr His Ile Ser Ser Lys Tyr Ser Tyr Leu Trp Arg Asn Phe Gly
45 1445 1450 1455

Ile Phe Trp Ile Tyr Ile Phe Phe Asn Ile Ile Ala Met Val Cys Val
1460 1465 1470

50 Tyr Tyr Leu Phe His Val Arg Gln Ser Ser Phe Leu Ser Pro Val Ser
1475 1480 1485

Ile Leu Asn Lys Ile Lys Asn Ile Arg Lys Lys Lys Gln
55 1490 1495 1500

Claims

1. A method for selectively modulating the activity of ABC transporters by influencing the dimerization of the nucleotide binding domains comprising the use of:

- 5 a) a polypeptide consisting of 5 to 50 amino acids comprising the D loop sequence of an ABC transporter,
b) a polypeptide consisting of the D loop sequence of an ABC transporter,
c) a peptide mimetic of any of the polypeptides of a) or b), or
d) an antisense peptide of the polypeptides of a) or b).

10 2. A method for selectively modulating the activity of ABC transporters by influencing the dimerization of the nucleotide binding domains according to claim 1 comprising the use of:

- 15 a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 1 to 43,
b) a polypeptide consisting of the amino acid sequence as represented in any of SEQ ID NOs 1 to 43 or a functional homologue thereof,
c) a peptide mimetic of any of the polypeptides of a) or b), or
d) an antisense peptide of the polypeptides of a) or b).

20 3. A method for selectively modulating the activity of an ABC transporter according to claim 1 or 2, wherein said ABC transporter belongs to the group of multidrug transporter/P-glycoproteins comprising the use of:

- 25 a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 1 to 3,
b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 1 to 3 or a functional homologue thereof,
c) a peptide mimetic of any of the polypeptides of a) or b), or
d) an antisense peptide of the peptide of a) or b).

30 4. A method for selectively modulating the activity of an ABC transporter according to claim 1 or 2, wherein said ABC transporter belongs to the group of the multidrug resistance associated proteins comprising the use of:

- 35 a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 4 to 15,
b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 4 to 15, or a functional homologue thereof,
c) a peptide mimetic of any of the polypeptides of a) or b), or
d) an antisense peptide of the peptide of a) or b).

40 5. A method for selectively modulating the activity of an ABC transporter according to claim 1 or 2, wherein said ABC transporter is a bacterial transporter comprising the use of:

- 45 a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39,
b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39, or a functional homologue thereof,
c) a peptide mimetic of any of the polypeptides of a) or b), or
d) an antisense peptide of the peptide of a) or b).

50 6. A method for selectively modulating the activity of an ABC transporter according to claim 1 or 2, wherein said ABC transporter is a fungal transporter comprising the use of:

- 55 a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 40, 41 or 42,
b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 40, 41 or 42, or a functional homologue thereof,
c) a peptide mimetic of any of the polypeptides of a) or b), or

d) an antisense peptide of the peptide of a) or b).

7. A method for selectively modulating the activity of an ABC transporter according to claim 1 or 2, wherein said ABC transporter is a protozoal transporter comprising the use of:

5 a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 2, 8 or 43,
 b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 2, 8, or 43, or a functional homologue thereof,
10 c) a peptide mimetic of any of the polypeptides of a) or b), or,
 d) an antisense peptide of the peptide of a) or b).

8. A method according to any of claims 5 to 7 wherein said ABC transporter is involved in bacterial, fungal or protozoal infection of a mammal.

- 15 9. A method according to any of claims 5 to 7 wherein said ABC transporter is involved in the induction of resistance to antibiotics or drugs in a mammal.

- 20 10. Method for preventing, treating or alleviating diseases associated with the functionality of a human ABC-transporter comprising the use of:

25 a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 1 to 36,
 b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 1 to 36, or a functional homologue thereof,
 c) a peptide mimetic of any of the polypeptides of a) or b), or,
 d) an antisense peptide of the peptide of a) or b).

- 30 11. Method for preventing, treating or alleviating diseases related with bacterial infections comprising the use of:

35 a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39,
 b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39, or a functional homologue thereof,
 c) a peptide mimetic of any of the polypeptides of a) or b), or,
 d) an antisense peptide of the peptide of a) or b).

- 40 12. Method for preventing, treating or alleviating diseases related with fungal infections comprising the use of:

45 a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 40 to 42,
 b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 40 to 42, or a functional homologue thereof,
 c) a peptide mimetic of any of the polypeptides of a) or b), or,
 d) an antisense peptide of the peptide of a) or b).

- 50 13. Method for preventing, treating or alleviating diseases related with protozoal infections comprising the use of:

55 a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 2, 8 or 43,
 b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 2, 8, or 43, or a functional homologue thereof,
 c) a peptide mimetic of any of the polypeptides of a) or b), or,
 d) an antisense peptide of the peptide of a) or b).

- 55 14. A method for identifying compounds which selectively bind to or selectively modulate the properties of ABC transporters, which method comprises:

- a) contacting a compound to be tested with a polypeptide as defined in any of claims 1 to 7, or with a polypeptide corresponding to the D loop of an ABC transporter,
b) detecting a diminution or inhibition of the activity of said ABC transporter, and,
c) identifying said compound.

- 5 15. A method for identifying compounds which selectively bind to or selectively modulate the properties of ABC transporters, which method comprises:
- 10 a) providing a yeast two-hybrid system wherein the nucleotide binding domains NBD1 and NBD2 of an ABC transporter are expressed, or
b) providing a mammalian expression system wherein the nucleotide binding domains NBD1 and NBD2 of an ABC transporter are expressed, or
c) providing a bacterial expression system wherein the nucleotide binding domains NBD1 and NBD2 of an ABC transporter are expressed, and,
15 d) interacting said compound with the complex formed by the expressed polypeptides as defined in any of a) to c),
e) inferring from the interaction between said compound and one of the nucleotide binding domains a modulation of the properties of said ABC transporter, and,
f) identifying said compound.
- 20 16. An isolated nucleic acid encoding a polypeptide comprising an ABC transporter D-loop as defined in claim 1 or 2.
17. A polypeptide encodable by a nucleic acid of claim 16.
- 25 18. A cellular host transformed with a nucleic acid encoding at least one nucleotide binding domain of an ABC transporter protein or a nucleic acid comprising a nucleic acid according to claim 16, said nucleic acid in an expressible format for use in a method of claim 15.
- 30 19. A pharmaceutical composition comprising at least one polypeptide of claim 1 or 2.
- 20 20. A compound obtainable by any of the methods of claims 14 or 15.
21. Use of a polypeptide as defined in claim 1 or 2 as a medicament.
- 35 22. Use of a compound according to claim 20 as a medicament.
23. Use of a polypeptide as defined in claim 17 or a compound obtainable by any of the methods of claims 14 or 15 for preventing, treating or alleviating diseases associated with the functionality of an ABC-transporter.
- 40 24. Use of a polypeptide as defined in claim 3 or 4 or a compound obtainable by any of the methods of claims 14 or 15 for treatment of cancer.
- 25 25. Use of a polypeptide according to claim 24 in combination with chemotherapy.
- 45 26. Use of a polypeptide as defined in claim 3 or 4 or a compound obtainable by any of the methods of claims 14 or 15 for the preparation of a medicine for treating cancer.
27. Use of a polypeptide as defined in claim 3 or 4 or a compound obtainable by any of the methods of claims 14 or 15 for treating resistance to drugs in a mammal.
- 50 28. Use of a polypeptide as defined in claim 3 or 4 or a compound obtainable by any of the methods of claims 14 or 15 for the preparation of a medicament for preventing, treating or alleviating diseases associated with drug resistance in a mammal.
- 55 29. Use of a molecule as defined in claim 5 or a compound obtainable by any of the methods of claims 14 or 15 for preventing, treating or alleviating diseases associated with bacterial infections.
30. Use of a molecule as defined in claim 5 or a compound obtainable by any of the methods of claims 14 or 15 for

EP 1 217 066 A1

the preparation of a medicament for preventing, treating or alleviating diseases associated with bacterial infections.

31. Use of a molecule as defined in claim 5 or a compound obtainable by any of the methods of claims 14 or 15 for
treating resistance to antibiotics in a mammal.

- 5 32. Use of a molecule as defined in claim 5 or a compound obtainable by any of the methods of claims 14 or 15 for
the preparation of a medicament for treating antibiotic resistance in a mammal.

- 10 33. Use of a molecule as defined in claim 5 or a compound obtainable by any of the methods of claims 14 or 15 as
an anti-bacterial agent.

- 15 34. Use of a molecule as defined in claim 6 or a compound obtainable by any of the methods of claims 14 or 15 for
preventing, treating or alleviating diseases associated with fungal infections.

- 20 35. Use of a molecule as defined in claim 6 or a compound obtainable by any of the methods of claims 14 or 15 for
the preparation of a medicament for preventing, treating or alleviating diseases associated with fungal infections.

- 25 36. Use of a molecule as defined in claim 6 or a compound obtainable by any of the methods of claims 14 or 15 as a
fungicide or anti-fungal agent.

- 30 37. Use of a molecule as defined in claim 7 or a compound obtainable by any of the methods of claims 14 or 15 for
preventing, treating or alleviating diseases associated with protozoal infections.

- 35 38. Use of a molecule as defined in claim 7 or a compound obtainable by any of the methods of claims 14 or 15 for
the preparation of a medicament for preventing, treating or alleviating diseases associated with protozoal infec-
tions.

- 40 39. Use of a molecule as defined in claim 7 or a compound obtainable by any of the methods of claims 14 or 15 as a
fungicide or anti-fungal agent.

30

35

40

45

50

55

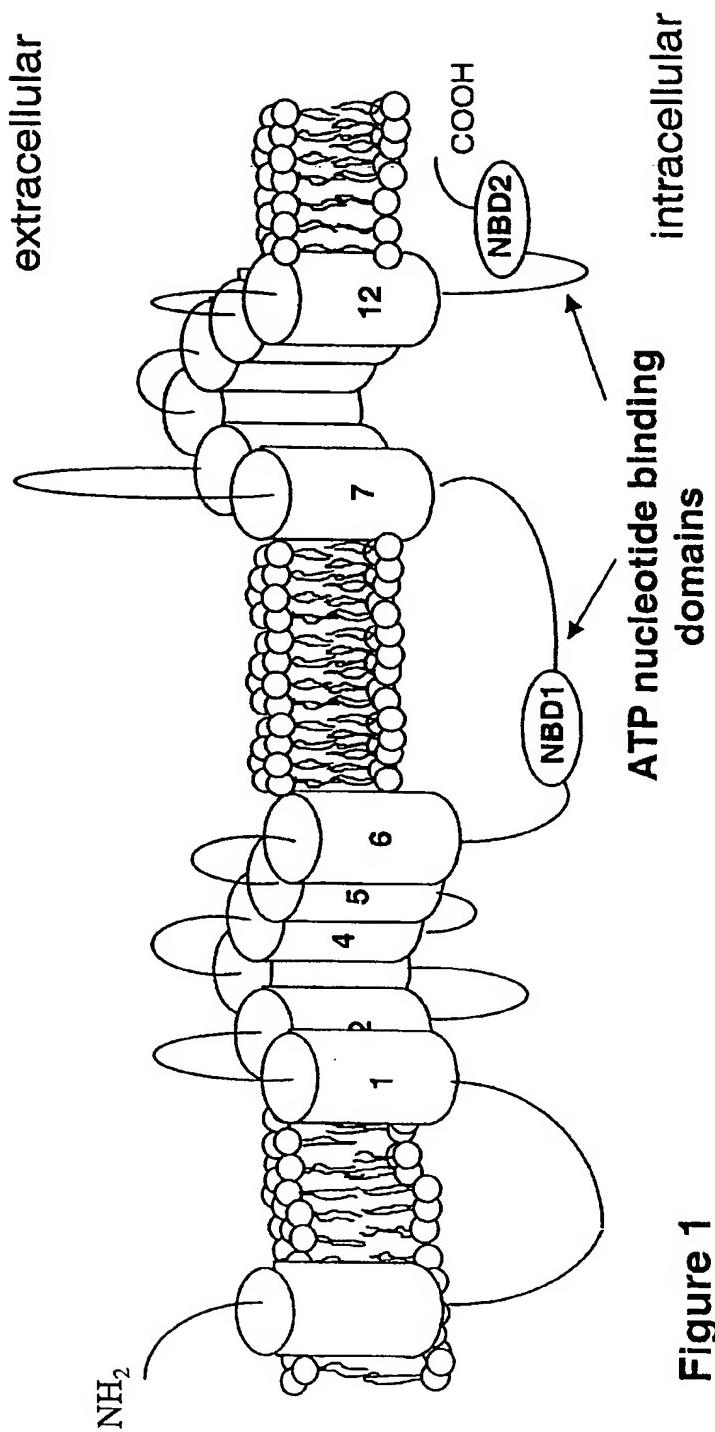


Figure 1

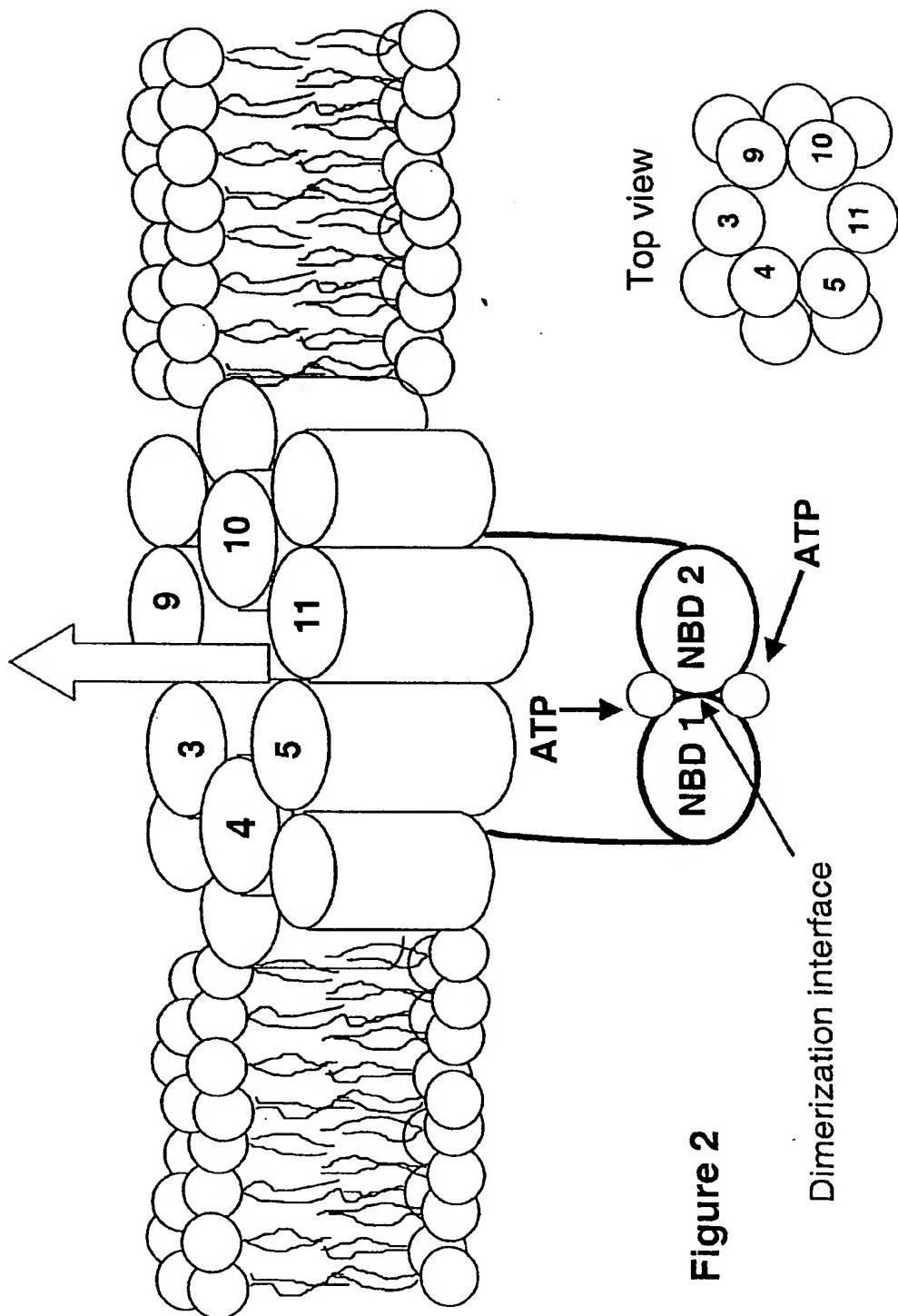


Figure 3 - 1
Figure 3 Human ABC Transporters (examples)

```
>ABC1=ABC1
MACWPQLRLLLWKNLTFRRLQTCQLLLEVAWPLFIFLILISVRLSYPPYEQHECHFPNKAMPSAGTLPW
VQGIICNANNPCFRYPTPGEAPGVGVNFNKSIVARLFSDARRLLYSQKDTSMKDMRKVLRTLQQIKKS
SSNLKLQDFLVDNETFSGFLYHNLSLPKSTVDKMLRADVLILHKVFLQGYQLHLSLCNGSKSEEMIQLG
DQEVSCLCGLPREKLLAAERVLRSNMDILKPLRTLNTSPPSKELAEATKTLLHSCTLAQELFSMR
SWSDMRQEVMLTNVNSSSSTQIYQAVSRIVCGHPEGGGGLKIKSLNLYEDNNYKALFGGGNGTEEDAET
FYDNSTTPYCNDLMKNLESPLSRIIWALKPILLVGKILYTPDPTPATRQVMAEVNKTFOELAVFHDLEG
MWEELSPKIWTFMENSQEMDLVRMLLDSRDNDHFWEQQLDGLDWTQAQDIAFLAKHPEDVQSSNGSVYT
WREAFNETNOAIRTISREMECVNUNLKEPIATEVWLINKSMEILLDERKFWGIVFTGITPGSIELPHHV
KYKIRMDIDINVERTNKIKDGYWDGPDRPDEMYWGGFAYLQDVVQEAIIRVLTGTETKKTGVYMOQ
MPYPCYVDDIFLRVMSRSMPFLMTLAWIYSTAVIYKGYEKEARLKETMRIMGLDNSILWFSPWFISSL
IPLLVSAGLLVILKLGNLPPYSDPSVVFVLSFAVVTILQCFLISTLFSRANLAAACGGIIFYFTLV
PYVLCVAWQDYVGFTLKIIFASLLSPVAFGFGCEYFALFEEQGIGVQWDNLFESEPVEEDGFNLTTSVMM
LFDTFLYVGWTYIEAVFEGQYGIIPREWYFPCFKTSYWFGEESDEKSHPGSNQKRISEICMEEPEHLKL
GVSIQNLVKVYRDGMVAVDGLALNFYEQITSLFLGHNGAGKTTMSILTGLFPPTSGTAYILGKDIRS
EMSTIRQNLGVCPQHNVLFMDLTVEBHWFYARLKGKHAEMEQMALDVGLPSSKLKSQTSQLSG
GMQRKLSVALAFVGGSKVWLLDEPTAGVDPYRSRRGIWELLKYRQGRFTIILSTHMDADEVLGDRIAII
SHGKLCVGSSFLKNQLGTGYYLTLVKDVESSLSSCRNSSTSVSYLKKEDESVSQSSSDAGLGSDHES
DYLTTIDVSAISNLIRKHVEARLVEDIGHELTYVLPYEAAKEGAFVELFHEDDRSLDGJISSYGISET
TLEEFLKVAEFGVDAETSDGTLPARNRRAFGDKQSCLRPFTEADADPNDSIDIPESRETDLLSGM
DGKGSYQVKGWKLTTQQQFALLWKRLLIARRSRKGFFAQIVLPVFCIALVPSLIVPPFGKYPSELEQ
PWMYNEQYTFVSNDAPEDITGTELLELNALTQDPMGFTRCMEGNIPDTPCQAGEEEWTATPVQTIMDLF
QNGNWMTMQNPSPACQCSDKIKKMLPVCPGAGGLPPQORKQNTADILQDITGRNISDYLVKTQVIIA
KSLKNKIWVNEFRYGGFSLGVNTQALPPSQEVNDATQMKKKHLKLAKDSSADRPLNSLGRFMIGLDTR
NNVKVWFNNKGWHAISSFLVINNAILRANLQKGENPSHYGITAENHPLNLTQQLSEVAAPMTTSVDVL
VSICVIFAMSFPVASFVFLIQERVPSKAHLQFISGVKPVIYWLNSFWWDMCNYVVPATLVIIIFICFQ
QKSYVSSTNLPVLLALLLILYGSITPLMYPASFVPKIPSTAYVVLTSVNLFIGINGSVATFVLELFTDN
KLNNINDILKSVFLIFPHFCLGRGLIDMVKNQAMADERFGENRFPVSPSLSDLVGRNLFAMAVEGVVF
FLITVLIQYRFFIRPRPVNAKLSPLNDEDEVRERQRILDGGQNIDILEKELTKIYRRKRKPADVRI
CVCIPPGECGFLLGVNGAGKSSTFKMLTGDTTVTRGDAFLNRNSILSNIHEVHQMGYCPQFDATIELL
TGREHVEFFALLRGVPEKEVGKVGEAIRKGLVKGYKEGYAGNYSGCKRKLSTAMALIGGPPVVFDE
PTTGMDPKARRFLWNCAVSVKEGRSVVLTSHMEECALCTRMAIMVNGRPRCLGSVQHLKNRFGDGY
TIVVRLAGSNPDLKPVQDFEGLAFPGSVPEKEHRNMIQQLPSSLSSLARIFSIILSQSKKRLHIEDYSV
SQTTLDQVFVNFAKDQSDDDHKLDSLHKNQTVVDVAULTSFLQDKEVKESV
```



```
>ABC2=ABC2
MGFLHQLQLLWKNVTLKRRSPWVLAIFIPLVLFILLGLRQKKPTISVKEVFPYTAAPLTSAGILP
VMQSLCPDGQRDEFGFLQYANSTVTQLLERLDRVVEEGNLFDPARPSLGESEALRQHLEALSAAGPGTS
GSHLDRSTVSSFSLDVARNPQELWRFLTQNLSPNSTAQQALLAARVDPPEVYHLLFGPSSALDSQGL
HKGQEPWSRLGGNPLFRMEELLAPALIEQOLTCTPGSGLERLITVPEOSOKGALQGYRDAVCSCQAAAR
ARRFSCLSALRNQLDVAKVSQQLGLDAPNGSDSSPQAPPYRQLQALLGDLLDAQVLQDVVDVL SALAL
LLPQGACTGRTPGPPASGAGGAANGTGAAGAVMGPNTAAEGAPSAAALATPDTLQGQCSAFVQLWAGLQ
PILCGNNRTIEPEALRRGNNMSSLGFTSKEQRNLLVHLMSTSNPKILYAPAGSEVDRVILKANETFAFV
GNVTHYAQWLNISAEIRSFLEQGRLQQHLRWLQQXVAELRHLPEALNLSLDELPPALRQDNFSLPSGM
ALLQQLDTIDNAACGWIQFMSKSVSDIFKGFPDEESIVNYTLNQAYQDNVTVPASVIFQTRKDCSLP
VHYXIRQNSSTEKTNEIRRAYERPGPNTGGRFYFLYGFVLIQDMMERAIIDTFVGHDVVEPGSYVQMF
PYPCYTRDDLFVIEHMMPCLCMVISWVYVSVANTIQHVAEKEHRLKEVMTKTMGLNNNAVHWVAFITG
QLSISVTAITALKYQVLMHSVVIWLFFLAVYAVATIMFCFLVSVLYSAKLASACGGIIFYFLSYVP
YMYVAIREEWAHDKITAFEXCITASLMSCTAFGLGSKFYALYEVAGVQIOWHTFSQSPVEGDDFNLLAV
TMLMDAVVYGLTWYIEAVHPGMYGLPRPWYFPPLQKSYWLGSGRTEAWEWSWPWARTPRLSVMEEQ
CAMESRRFEETRGMEEEPTHLPLVVCVDKLTKVYKDDKLLALNKLSLNLYENQVVSFLGHNGAGKTTM
SILTGFPPSTSATIYGHDIRTEMDEIRKLNLMCOPQHNLFDRLTVEEHWFYSLRSKMSAQEERREM
DKMIEDLELSNKRHSVLQTLSSGMKRLKSLVAIFAVGGSRAIILDEPTAGVDPYARRAIWDLILKYKPG
TILLSTHMHDEADLLGDRIAITSHGKLCGSPPLFLKGTYGDGYRILTUVKRPAEPPGQEPGLASSPG
RAPLSSCSELQVSQFIRKHVASCLLVSSTDSTELSYILPSEAAKGAFERLFQHLERSLDALHLSFGML
DTTLEEVFLKVSEEDQSLENSEADVVKESRKDVLPAGAEGPASGEGHAGNLLARCSELTSQASLQSASSVG
SARGDEGAGYTDVYGDYRPLFDNPQDPDNVSLOEVEAALSRVGQGSRKLDGGWLVRQFHGLLVKRPH
CARRNSKALFSQILLPAFFVCVAMTVALSVPEIGDLPPLVLSPSQYHNTQPRGNFIPYANEERREYRL
RLSPDASPQQLVSTFRLPSGVGATCVLSPANGSLGPTLNLSSESRLLAARFFDSMCLESFTQGLPLS
NFVPPPPPSPAPSDSPASPDLEDQAWNVLSPPTAGPEMWTAPSPLPRLVREPVRCTCSAQGTGFSCPSSV
GGHPQMRVVTGDLTDITGHNVSEYLLFTSDRFRLHRYGAITFGNVLKSIPASFGTRAPPMVRKIAVR
RAAQVFYNNKGYHSMPTYLNSLNMAILRANLPKSKGNPAAYGITVNHPMNKTASLSDLYLOGTDVV
IAIFIIVAMSFVPAFVFLVAEKSTAKHLQFVSGCNPIIYWLANYVWDMNLNVLPATCCVIIILFVFD
```

Figure 3 - 2

LPAYTSPTNFPAVLSLFLLYCGWSITPIMYPASFWFEPSSAYVFLIVINLFIGITATVATFLLQLFEHD
 KDLKVVNSYLXSCFLIFPNYNLGHLMEMAYNEYINEYYAKIGQFDKMKSPFEWDIVTRGLVAMAVEGV
 VGFLLTIMCQYNFLRRPQRMPVSTKPVEDDVVASERQRVLRGDAANDMVKIENLTKVYKSRKIGRILA
 VDRLCGVRPGECFGILGVNAGKSTFKMLTGDESTCGEAFVNCHSVLKELLQVQOSLGCPQCDAL
 FDELTAREHLQYTRLRGISWKDEARVVKALELTKYADKAGTYSGGNKRKLSTAIALIGYPAFI
 FLDERTTGMDPKARRFLWNLLDILKTGRSVLTSHSMECEALCTRLAIMVNCLRCLGSIQHLLKNRF
 GDGYMITVRTKSSQSVDVVRPFNRNFPEAMLKERHHTKVQYQLKSEHISLAQVFSKMEQVSGVLGIED
 YSVSQTLDNVFVNFACKQSDNLEQQETEPPSALQSPLGCLSLLRPRSAPELRALVADEPEDLTD
 EGLISFEEERAQLSFNTDTLC

>ABC43=ABC-C

MAVLRLQALLLWKNYTLQKRKVLVTVLELPLPLLFPGLI.IWLRLKIQSENVNPATIYPGQSIQELPLFF
 TFPPIPGDTWELAYTPSHSDAAKTVTETVRRALVINMRVRFPSKDFEDYIYRDNCSSVLAAVVFEHP
 FNHSKEPLPLAVKYHLLRFSYTRRNYMWTQTSFFLKETEGWHTTSFLPPLPPNGPRELTSPDGGEPEGYI
 REGFLAVQHADRAIMEYHADAAATRQLPQLTWTIKRPYPPFLADEPFLVAIYQOLPLLLLSSFTYTAL
 TIARAVVQEKKRKEYMRRMGLSWSLHSAWFLFFPLLIASAFTMFLFCVVKVPNVAVLSRSDPPL
 VLAFLLCFAISTISPSFMVSTFSKANMAAAFCGGFLYFFTPIAIPPFVAPRYNWMTLSQKLCSCLLSNVA
 MAMGAQLIGKFEAKGMGIQWRDLSSPVNDDFCFGQVGLGMLLDSVLYGLVWMEAVFPQGQFVQP
 WYFFIMPSYWCGKPRAVAGKEEEDSDPEKALRNEYFEEAPEDLVAGIKIKHLSKVFRVGNKDRAVRDL
 NLNLNLEGGITVLLHGNGAKTTTMSLTLGFLPPPTSGRAYISGYEISQDMVQIRKSLGLCPQHDLILEDNL
 TVAEHLYFYAQALKLGSRKCPPEVKQMLHIIGLEDKWNSRSRSLSGGMRRKLSIGIALQSKVLLID
 PTSGMDAISRAIWDLILQRQKSRTIVLTHPMDEADLLGDRIAIMAKGELQCCGSSLFLKQKYGAGYH
 MTLVKEPHCNPDISQLVHHVNPATLESSAGAELSFILPRESTHRFEGFLAKLEKKQKELGIAFGAS
 ITTMEEVFRLVGKLVLDSSMDIQAIQLPALQYQHERRASDWAVDSNLCGAMDPSDGIGALIEEERTAVKL
 NTGLALHCQQFWMLKKAWSREWVMQAQVLVPLTCVTLALLAINYSSELFDPPMLRLTGEYGR
 VVPPFVPGTSQLGQLESEHKLDALQAEQGPREVLGDLFIRASVEGGFNERCLVAASFRDVG
 TVVNAFLNNQAYHSPATALAVVDNLLFKLLCPHASTVVSNEFPQPRSLQAAKQDFNEGKGFIDALNL
 LFAMAFLASTFSILAVSERAVQAKHVQPVSGVHVASFWLSALLWDLISLIPSLLLVVFKAFDRAFT
 RDGHMADTLLLRLYQWAIIPMLYLMNFFLGAATAYTRLTIFNLSGIAFLMVITIMRIPAVKLEELS
 KTLDHVFLVLPNHCGLMAVSSPYENYCTTSSEVAAHYCKKYNIQYQENFYAWSAPGVGRFVASMA
 ASGCAYLILLFLIETNLLQRLRGILCALRRRTLTELYTRMPVLPEDQDVADERTRILAPSPDSLLHTP
 LIKELSKVYEQRVPLLAUDRILSLAVQKGECFGLLGNGAKTTTPKMLTGEESLTSQDAFVGHHRISS
 DVGVKVRQIGYCPQFDALLDHMTGREMLVMYARLRGI PERHIGACVENTLRGLLEPHANKLVRTYSGG
 NKRLKSTGIALIGEPAVIFLDEPSTGMDPVARARLLWDTVARARESGKAI ITSHSMECEALCTRLAIM
 VQQQFKCLGSPQHLKSKFGSGYSLRAVKQSEGQEALEEFKAFVDLTFPGSVLEDEHQGMVHYHLPGRD
 LSWAKVFGILEAKEKYGVDDYSVSQISLEQVFLSFAHLQPPTAEEGR

>ABC44=ABC-R

MGFVROJQLLWKNWTLRKQKIRFVVELVWPLSLFLVLIWLRLNANPLYSHHECHFPNKAMPSAGMLPW
 LQGIFCNVNNPCFQSPTPGESPGIVSNYNNISLARVYRDFQELLMNAPESQHGRIWTELHILSQFMDT
 LRTHPERIAGRGRIRIDLKDEETLTFLIKNIGLSDSVVYLLINSQVRPEQFAHGVPLAKDIA
 CSE ALLERFIIFSQRRGAKTVRALCSLSQGTLOQWIEDTLYANVDFFKLFRVLPPLDDRSQGINLRSWG
 LSDMSPRIQEFIHRSMSQDLLWVTRPLMQNGGPETFTKLMGILSDLGYPEGGGSRVLSFNWYEDNNY
 KAFLGIDSTRKDPSYDRRTSFCNALIQSESPLTKIAWRAAKPLLMGKILYTPDS9AARRILKNA
 NSTFEELEHVRKLVKAWEVGPQIWIYFFDNSTQMNMRDTLGNPTVKDFLNRLQGE
 EGITAEEAILNFLY KGPRESQADMMANFDWRDIFNTIDRTLRLVNQYLECLVLDKFESYND
 EQLTQRALSLLEENMFWAGVV FPDMYFWTSSLLPPhVVKYKIRMDIDVVEKTNKIKDRYWD
 SGPRADPVEDFRIWGGFAYI QDMVEQGITR SQVQAEAPVGIFYLQQM
 PFCVDDSMIILNRCFPIFMVLAWIYVSMTVKISIVLEKE
 RLKETLKKNQG VSNAVINCTWFLDSFSIMSMSIPLLTIFIMHGR
 HSDPFILFLFLAFSTATIMLCFLSTFSKAS LAAACSGVIYFTLPHILCFAWQDRM
 TAELKKAVSLLSPVAFGFT
 EYLVRFEEQGLGLQWSNIGNSP TEGDEFSPILLSM
 QMMLLDA
 CYGLLAWYLDQVFCGDYGTPLPWYFLQESWLS
 SGEGCSTREERALEKT EPLTEETEDPEHPEGI
 HDSPFEREHPGWVPGVCVKNL
 KIPEPCGRPAVDRLN
 ITFYENQITAFLGHNG AGKTTT
 LSITLGLPPTSGTVLVGGDI
 ETSLDAVRSQSLGMCPQHN
 ILFHHLTVAEHMLFYAQLKGKSQ
 EEAQLEAMEAL
 DEDTGLHKKRNE
 EAQDLSGGM
 QKRLSVA
 IAFVGD
 AVK
 QV
 R
 S
 R
 I
 WD
 LL
 LKYRSGRTI
 IMP
 THHM
 DEAD
 HQGD
 RIA
 IA
 Q
 G
 R
 C
 T
 P
 A
 H
 V
 D
 L
 T
 P
 E
 V
 Q
 L
 D
 G
 D
 V
 N
 E
 L
 M
 D
 V
 L
 H
 H
 V
 P
 E
 A
 K
 L
 V
 E
 C
 I
 C
 Q
 E
 L
 I
 F
 L
 L
 P
 N
 K
 F
 K
 H
 R
 A
 Y
 A
 S
 L
 F
 R
 E
 E
 L
 E
 T
 L
 A
 D
 L
 G
 L
 S
 S
 F
 G
 I
 S
 D
 T
 P
 L
 E
 E
 I
 F
 L
 K
 V
 T
 E
 D
 S
 D
 G
 P
 L
 F
 A
 G
 G
 A
 Q
 Q
 K
 R
 E
 N
 V
 P
 R
 H
 P
 C
 L
 G
 P
 R
 E
 K
 A
 G
 Q
 T
 P
 Q
 D
 S
 N
 V
 C
 S
 P
 G
 A
 P
 A
 A
 H
 P
 C
 Q
 O
 P
 P
 P
 E
 C
 P
 C
 P
 Q
 L
 N
 T
 G
 P
 L
 V
 L
 Q
 H
 V
 Q
 A
 L
 L
 V
 K
 R
 F
 Q
 H
 T
 I
 R
 S
 H
 K
 D
 F
 L
 A
 Q
 I
 V
 L
 P
 A
 T
 F
 V
 P
 L
 A
 M
 L
 S
 I
 V
 I
 L
 P
 F
 G
 E
 P
 A
 L
 T
 L
 H
 P
 W
 I
 Y
 G
 Q
 Q
 Y
 T
 F
 F
 S
 M
 D
 E
 P
 G
 S
 E
 Q
 F
 T
 V
 L
 A
 D
 V
 L
 L
 N
 K
 P
 G
 F
 N
 R
 C
 L
 K
 E
 G
 W
 L
 P
 E
 Y
 P
 C
 G
 N
 S
 T
 P
 W
 K
 T
 P
 S
 V
 S
 P
 N
 I
 T
 Q
 L
 F
 Q
 K
 Q
 W
 T
 Q
 V
 N
 P
 S
 P
 C
 R
 C
 S
 T
 R
 E
 K
 L
 T
 M
 L
 P
 E
 C
 P
 E
 G
 A
 G
 G
 L
 P
 P
 P
 Q
 R
 T
 Q
 R
 S
 T
 E
 I
 L
 Q
 D
 L
 T
 D
 R
 N
 I
 S
 D
 F
 L
 V
 K
 T
 P
 A
 I
 R
 S
 S
 L
 K
 S
 K
 F
 W
 V
 N
 E
 Q
 R
 Y
 G
 G
 I
 S
 I
 G
 G
 K
 L
 P
 V
 V
 P
 I
 T
 G
 E
 A
 L
 V
 G
 F
 L
 S
 D
 L
 G
 R
 I
 M
 N
 V
 S
 G
 G
 P
 I
 T
 R
 E
 A
 S
 K
 E
 I
 P
 D
 F
 L
 K
 H
 L
 E
 T
 E
 D
 N
 I
 K
 V
 W
 F
 N
 N
 K
 G
 W
 H
 A
 L
 V
 S
 F
 L
 N
 V
 A
 H
 N
 A
 I
 R
 R
 S
 P
 E
 E
 Y
 G
 I
 T
 V
 W
 V
 F
 L
 D
 I
 M
 N
 Y
 S
 V
 S
 A
 G
 L
 V
 V
 G
 I
 F
 I
 G
 F
 Q
 K
 K
 A
 Y
 T
 S
 P
 E
 N
 L
 P
 A
 L
 V
 A
 L
 L
 L
 Y
 G
 W
 A
 V
 I
 P
 M
 M
 Y
 P
 A
 S
 F
 L
 F
 D
 V
 P
 S
 T
 A
 Y
 V
 A
 S
 C
 A
 N
 L
 F
 I
 G
 I
 N
 S
 S
 A
 I
 T
 F
 I
 L
 E
 F
 D
 N
 N
 R
 T
 L
 L
 R
 F
 N
 A
 V
 L
 R
 K
 L
 L
 I
 V
 F
 P
 H
 F
 C
 L
 G
 R
 G
 L
 I
 D
 L
 A
 S
 Q
 A
 V
 T
 D
 V
 Y
 A
 R
 F
 G
 E

Figure 3 - 3

EHSANPFHWDLIGKNLPMAMVVEGVVYFLTLVQRHFFLSQWIAEPTKEPIVDEDDDVABERQRITGG
 NKTDILRLHELTKIYLGTSSPAVDRLCVGVRPGEFGLLGVNAGKTTFKMLTGDFTVTSGDATVAGK
 SILTNISEVHQNMGYCPQFDAIDELTLTGREHLYLARLRGVPAEEIEKVANNSIKSLGLTVYADCLAGT
 YSGGNKRKLSTAIALIGCPPVLLEDEPTGMDPQARRMLWNVIVSIIRKGRAVVLTHSMEECEALCTR
 LAIMVKGAFCRMCGTIQHLKSFGDGIVTMKIKSPKDLLPDLN2VEQFFQGNFPGSVQRERHYNMLQF
 QVSSSSLARIFQLLSHKDSLLIEEYSVTTLDQVFVNFAKQQTESHDPLPLHPRAAGASRQAQD

>ABC A7=ABCX

MAFWTQLMILLWKNFMYRRRQPVQLLVEILLWPLFLFFILVAVRHSHPPLEHHCHFPNKPLPSAGTPW
 LQGLICNVNNTCPQLTPGEEPGRLSNFDNSLVSRLIADARTVLGCGASAHRTLAGLCKLIATLRAARST
 AQPQPTKQSPLPEPPMLDVAELLTSLLRTESLALGQAEPLHSLLEAAEDLAQELLAIRSLVELRALL
 QRPRGTSGPLLEALCSVRGPSSVTGPSLNLWYEASDLMELVGQBPESALPDSSLSPACSELIGALDS
 HPLSRLLWRRLKPLILGKLLPAPDTPTFRKLMAQVNRTFBELTLLRDVREVMWEMLGPRIFTFMNDSSNV
 AMLQRLLQMDEGRQRQPRPGGRDHMEALRSFLDPGSGGSWQDAHVGHLVGTLCRVTECLSLDKLEA
 APSEALVSRALQLLAEHRFWAGVVFGLPVEDSSDPTHEPTPDLGPGHVRKIRMDIDVVTTRNKKDRF
 WDPPGAADPLTDLRYWGGPVYQLDVERAARVLSGANPRAGLYLQMQPYPCYVDDVFLRVLRSRLP
 FLTLAWIYSTLTVKAVVREKETRLRDTMAMGLSRAVLWLWGFLSCLGPFLSALLVVLKLDILP
 YSHPGVVFPLFLAAFAVATVQSFLLSAFSRANLAAACGLAYFSLYLPYVLCVAWRDRLPAGGRVAAS
 LLSPVAFGFCESLALLEEQQEGAQWHNVGTRPTADVFLAQVSGLILLDAALYGLATWYLEAVCPGQY
 GIPPEPWNPFPFRSWSWCGRPPKSPAPCPTPLDPKVLVIEAPPGLSPGSVRSLEKRFPGSPQPALRGLS
 LDFYQGHITAFLGHNGAGKTTLSILSGLFPSCGSASFILGHDRVSSMAIRPHLGVCPCYQNVLFDMLT
 VDEHVVWVYGRLKGLSAAVVGPEDRLLQDVGLVSKQSVQTRHLSGGMQRKLSVATAFVGGSQVVIIDEP
 TAGVDPASRRGIWELLKYREGRTLILSTHILDEAEELLGDRVAVVAGGRLLCCGSPFLRRLHGSYYL
 TLVKARLPLTTNEKAUTDMEGSDTRQEKKNGSRSVTPQOLLQHNVPGARLVEERLPHELVLVLP
 YTGAHDGCFRELDTRLAELTGYSIDTSLEEFLKVVEECAADTMEDGSCGQHLCCTGLAGLD
 VTLRLKMPPQETALENGEPAGSAPETDQGSGPDAVGRVQGWALTRQQLALLKRFLLARRSRRGLFAQ
 IVLPALFVGLALVFLSIVPPFGHYPALRLSPMTYGAQVSFSEDAPGDPGRARLLEALLQZAGLEEPVV
 QHSSHRFSAPEVPAEVAKVLASGNWTPESPSPACQCSPQGARRLLPDCPAAAGGPPPPQAVTGSGEVVQ
 NLTGRLNLSDFLVKTYPRVLRQGLKTFKWKVNEVRYGGFSLGGRDPGLPSQELGRSVEELWALLSPPLPGG
 ALDRVNLKNTAWHSLDAQDSLKWFNNKGNSMVAFVNRSNAILRHLPPGRARHAAHSTITLNHPLN
 LTKEQLPEALMASSDVLSICVFMSEVPAFTLVLIEERVTRAKHLQMGGLSPTLYWLGNFLWD
 MCNYLVPCAIVVLIFLAFQRAYVAPANLPALLLILLYGWSITPLMYPASFFFSPVSTAYVVLTCINL
 FIGINGSMATFVLELFSDQKLQEVSRILKQVFLIPPHFCLGRGLIDMVRNQAMADAERLGDQFQSP
 RWEVVGKNIILAMVIQGLPFLFTLLOHRSQLLPQPRVRSLPLGEDEDEDVARERERVVQGATQGDVLV
 LRNLTKVYRGQRMVPAVDRLCLGIPGECFGLLGVNAGKTSFMRVTDLTSRGEAVLAGHSVAREPS
 AAHLSMGYCPOSDAIFELLTGREHLELLARLRGVPEAQVAOTAGSGLARLGLSWYADRPGACTYSGGNKR
 KLTALALVGDPAAVFLDEPTGMDPSARRFLWNSLLAVVREGRSVMTLSHMEECEALCSRЛАIMNG
 RFRCLGSPQHLKGRFAAGHTLTLRVPAAQSPAAEFPSSELREAHGGRRLRFQLPPGRCALARV
 FGELAVHGAEHGVEDFSVSQTMLEEFLYFSKDQGKDEDTEEQKEAGVGVDPPAPGLQHPKRVSQFLDDP
 STAETVL

>ABC A8

MRKRKISVCQQTWALLCKNFKKWRMKRESLMEWLNSSLILCLYIYPHSHQVNDFSSLTMDLGRVDT
 FNESTRFSVYVPTVTNTIQMNMKVASTPFLAGKEVLPDEESIKEPTNYPEEIVRVTFTNTYSHLK
 PLLGHGMPAKKEHDHTAHCYETNEDVYCEVSFWKEGFVALQAAINAIIIEITTNHSVMEELMSVTGK
 NMKMHSHFIGQSVITDLYLSCIIISFSSFIYYASVNMTRERKRMKALMTMMGLRDSAFLWSWGLLYAGF
 IFIMALFLALVIRSTQFIIISLGFMVVFSLFLYGLSLVALAFLMSILVKKSLTGLVVFLLTVFWCLG
 FTSLYRHLPALEWILSLLSPFAFMLGMAQLLHLDYDLSNAFPHPSDGSNLIVATNFMLAFTCLYLA
 LAIKEYKEPKLNEYGHRRPLFLKSSFSQTLQKTDHVVALEDEMADPSFHDSFQEAPPEFQGKEAIRR
 NVTKEYKGKPKDIBALKDVLFDIYEGQITAIILGHSGACKSTLNLQSLSPVTKGSVTIYNNKLSEMAD
 LENLSKLTGVCPOSNVQDFLTVRENRLFAKIKGILPQEVDKEIFLDEPTAGLDPSRQHVWNLLKE
 RKTDRVILFSTQFMDEADILADRKVFLSQGKLCAGSSLFLKKWIGYHLSLQLNEICVEENITSVK
 QHIPDAKLSAKSEGKLIYTPLERTRNKEPELYKDLDSYPDLGTTENGVSMTTLNNEVFLKLEGKSTINES
 DIAITLGEVQAEKADDTERLVEEMEQVLSNLKMRKTIGGVALWRQQICIAARVLLKLKHERKALLALL
 ILMAGFCPLLVEADTVMKIVYQNSYTWELSPHLYFLAPGQOPHDPLTQLIINKTGASIDDFIQSVEHQNI
 ALEVDAFGTRNGTDDPSYNGAITVCCNEKNYSFLSACNAKRLNCFPVLMDEVSNGLGMVKPSVHIRTE
 RSTFLENGQDNPIGFLAYIMFWLVLTSSCPPIIAMSSIDDYKRNARSQRLRISGLSPSAYWFGQALVDS
 LYFLVVFIFYLMSYISNFEDMLLTIIHIIQIPCAVGYSFSLIFMTVVISFIFRKGRNNSGIWSFCFVV
 TVFSVAGFAPSIFEDSIDIPTFLIPATMIGCLFLSSHLLFSSLSEERMDVQPFVFLIPFLHFIIF
 LFTRLRCLEWKFGKKSMDPFRISPRSSDVCQNPEEPEGEDEDVQMERVTANALNSTNFDEKPVIIIA
 SCLRKEYAGKRGKCFSKRKNKIAITRNSVFCVRKGEVLLGHNAGKSTSIVTGDTPTAGQVLLKG
 SGGGDALEFLGYCPCQENALWPNLTVRQHLEVAVAKGLRKGDAEVAITRLVDALKLQDQLKSPVKTLS
 GIKRKLCFVLSILGNPSVLLDEPSTGMDPECQQQMWAIRATFRNTERGALLTHYMAEAEAVCDRVA
 IMVSGRLRCIGSIQHLKSFGKDYLLEMVKVNLAQVEPLHAEILRLFQQAARQERYSSLMVYKLPVEDV
 QPLAQAFFKLEVKQSFLEEYLSQSITLEQVFLELSKEQELGDFEEDFDPSVWKLLPQEEP

Figure 3 - 4

>ABCBl=MDR1 (multidrug resistance protein 1 or P-glycoprotein)
MDLEGDRNGGAKKKNNFKLANNKSEKDKEKKPTVSVFSMFRYSNWLKDLYMVGTAAIIHGAGLPLMM
LVFGEMLTDIFANAGNLEDLMSNITNRSDINTGFFMNLLEEDMTRYAYYSGIGAGVLVAAYIQVSFWCL
AAGRQIHKIRKQFFHAIMRQEIGWFDVHDVGELNTRLTDDVSKINEGIGDKIGMFQSMTPTGFIVG
FTRGWKLTLVILAISPVGLSAAVWAKILSSFTDKELLAYAKAGAVAEEVLAIRTVIAFGQQKKELER
YNKNLLEEAKRIGTKKAITANISIGAAFLIIASYALAFWYGITLVLSGEYSIGQVITVFSVLIGAFSVG
QASPSIEAFANARGAAYEIFKIIDNKPSKSCHPKDNLGNLFRNHFSPSRKEVKILKGLNL
KVQSGQTVALVNGSCCGKSTTVQLMQRLYDPTEGMVSVDQDIRTINVRFLREIIGVVSQEPVLFATTI
AENIRYGRENTMDEIEKAVKEANAYDFIMKLPHKPDTLVGERGAQLSGGQKQRIAIARALVRNPKILL
LDEATSALDTESEAVVQVALDKARKGRTTIVIAHRLSTVRNAADVAGFPDDGVIVEKGHNDELMKEGIY
FKLVTMOTAGNEVELENAADESKSEIDALEMSSNSRSSLIRKRSTRRSVRGSQAODRKLSKTEALDES
IPPVSFWRIMKLNLTWEFGCIAINGLQPAFAIFISSKIIGVFTRIDDPETKRQNSNLFSLLFL
ALGIISFITFELQGFTFGKAGEELTKRLYMFVRSMLRQDVSWFDDPKNTTGAATRLANDAAQVKGAI
GSRLAVITQNTIANLGTGIIISFIYQWQLTLLLAIVPIIAIAGVEMKMLSGQALKDKKELEGSGKIA
EATENPRTVVSLSLTQEKFEMHYAQSLQVPPRNSLRKAHIFGITFSFTQAMMYFSYAGCFRGAYLVAHK
LMSFEDVLLVFSAVVFGAMAVGQVSSFAPDVAKAKISAHHIMIIEKTPPLIDSCTEGLMPNTLEGNT
FGEVVFNYPTRPDIPVQLQGLSLEVKGQTLALVGGCGKSTVVQLERFYDPLAGKVLLDGKEIKRLN
VQWLRAHLGIVSQEPILFDCSIAENIAYGDNSRVSQEEIVRAAKEANIHAFIESLPNKYSTKVGDKGT
QLSGGQKQRIAIARALVRQPILLDEATSALDTESEKVLQVALDKAREGRTCIVIAHRLSTIQNADLI
VVFQNQGRVKEHGTHQQLAQKGIYFSMVSQAGTKRQ

>ABCBl=MDR1 (transporter associated with antigen processing)
MAELLASAGSACSWDFPRAPPSPPPPASRGGLGGRSFRPHRGAESPRPGDRDGVRVPMASSRCPAP
RGCRCPLPGASLAWLGTVLLLADWVLLRTALPRIFSLVPTALPLLRVWAVGLSRWAVLWLGACGVLR
TVGSKSENAGAQGWLAALKPLAAALGLALPGLALFRELISWGAPGSAADSTRLLHWGSHPTAFVVSYAAA
LPAAALWHKLGSLWVPGGGSGNPVRRLGCLSETRRSLFLVLLVLSLGEAMAIPFFTGRLTDWIL
QDGSADTFTRNLTLMSENLSLFLWYLVRGLCLLGIMLWGSVSLTMVTLITLPLLFLPKVKGWYQLLEV
SRVTEDTSTLSDSLSENLSLFLWYLVRGLCLLGIMLWGSVSLTMVTLITLPLLFLPKVKGWYQLLEV
QVRESLAKSSQVAIEALSAMPTVRSFANEEGEAQKPREKLQEIKTLNQKEAVAYAVNSWITSISGMLLK
VGILYIGGOLVTSGAVSSGNLVTFLYQMOFTQAVEVLLSIYPRVQAVGSSEKIFEYLDRTPRCPSG
LLTPLHLEGLVQFQDFVSPAYPNRPDVLLVQGLTFTLRPGEVTAALVCPNGSGKSTVAALLQONLYQPTGGQ
LLLDGKPLPQEYEHRYLHRQVAAVGQEPQVFRSLQENIAYGLTQKPMEEITAAAVKSGAHFISGLPQ
GYDTEVDEAGSQLSGGQRQAVALARALIRKPCVLILDATSALEANSQLOVEQLLYESPERYSRSVLLI
TQHLSLVEQADHILFLEGGAIREGGTHQQLMEKKGYWAMVQAPADAPE

>ABCBl=MDR1 (transporter associated with antigen processing)
MAELLASAGSACSWDFPRAPPSPPPPASRGGLGGRSFRPHRGAESPRPGDRDGVRVPMASSRCPAP
RGCRCPLPGASLAWLGTVLLLADWVLLRTALPRIFSLVPTALPLLRVWAVGLSRWAVLWLGACGVLR
TVGSKSENAGAQGWLAALKPLAAALGLALPGLALFRELISWGAPGSAADSTRLLHWGSHPTAFVVSYAAA
LPAAALWHKLGSLWVPGGGSGNPVRRLGCLSETRRSLFLVLLVLSLGEAMAIPFFTGRLTDWIL
QDGSADTFTRNLTLMSENLSLFLWYLVRGLCLLGIMLWGSVSLTMVTLITLPLLFLPKVKGWYQLLEV
SRVTEDTSTLSDSLSENLSLFLWYLVRGLCLLGIMLWGSVSLTMVTLITLPLLFLPKVKGWYQLLEV
QVRESLAKSSQVAIEALSAMPTVRSFANEEGEAQKPREKLQEIKTLNQKEAVAYAVNSWITSISGMLLK
VGILYIGGOLVTSGAVSSGNLVTFLYQMOFTQAVEVLLSIYPRVQAVGSSEKIFEYLDRTPRCPSG
LLTPLHLEGLVQFQDFVSPAYPNRPDVLLVQGLTFTLRPGEVTAALVCPNGSGKSTVAALLQONLYQPTGGQ
LLLDGKPLPQEYEHRYLHRQVAAVGQEPQVFRSLQENIAYGLTQKPMEEITAAAVKSGAHFISGLPQ
GYDTEVDEAGSQLSGGQRQAVALARALIRKPCVLILDATSALEANSQLOVEQLLYESPERYSRSVLLI
TQHLSLVEQADHILFLEGGAIREGGTHQQLMEKKGYWAMVQAPADAPE

>ABCBl= MDR3= Multidrug Resistance Protein 2 and 3 or P-glycoprotein
3
MDLEAAKNGTAWRPTSAEGDFELGISSKQKRKKTKTVMIGVLTFRYSDWQDKLFMSLGTIMAIAGHS
GLPLMMIVFGEMLTDKFVDTAGNFSFPVNFSLSLNPKGILEEEMTRYAYYSGLGACVLVAAYIQVSFW
TAAAGRQIIRKIRQKFFHAIROLRQEIGWFDINDTTELNTRLTDDISKISEGIGDKVGMFFQAVATFFAGFI
VGFIRGWKLTLVIMAISPILGLSAAWAKILSAFSDEKELAAYAKAGAVAEEALGAIRTVIAFGQQNKE
ERYOKHLENAKEIGIKKAIASANISMGIAFLIIYASALAFWYGSTLVISKEYTIGNAMTVFFSILIGAF
SVGQAAPCIDAFANARGAAYVIFDIIDNNPKIDSFSERGHKPDSIKGNLEFNDVHSYPSRANVKILKG
LNLKVGSGQTVALVGGCGKSTTVQLIQLYDPEGTINIDGQDIRNFNVNLYREIIGVVSQEPVLFS
TTIAENIICYGRGNVTMDEIKKAVKEANAYEFIMKLPQKFDTLLVGERGAQLSGGQKQRIAIARALVRNPK
ILLDEATSALDTESEAEVQAAALDKAREGRTTIVIAHRLSTVRNAADVAGFEDGVIVEQGSHSELMKKE
GVYFKLVLNMQTSGQIQSEEFELNDEKAATRMAPNGWKSRLFRHSTQKNLKNSOMCQSLDVTDGLEA
NVPPVSFLKVLKLNKTEWVYFVVGTVCAIANGLQPAFSVIFSEIIIAIFGPDDAVKQQKCNIIFSLIIF
FLGILISFTFFLQGFTFGKAGEILTRRLRSMAFKAMLQDMWSFDDHKNSTGALSTRLATDAAQVQGAT
GTRLALIAQNTIANLGTGIIISFIYQWQLTLLLAIVVPIAVSGIVEKLLAGNAKRDKELEAAGKIA

Figure 3 - 5

EAIEINTVVSLLTQERKFESMYVEKLYGPyRVFSAIVFGAVALGHASSFAPDYAKAKLSAAHLMFLFER
 QPLIDSYSEEGLKPDKFEGNITFNEVVNVYPTTRANPVQLQGLSLEVKKQTLALVGSSGCGKSTVVQLL
 ERFYDPLAGTVLLDGQEAKKLNVQWLRAQLGIVSQEPILFDCSIAENIAYGDNSRUVSQDEIVSAAKAA
 NIHPPIETLPHKYETRVGDKGTQLSGGQKQRRIATARALIRQPOILLDEATSALDTESEKVVQEALDKA
 REGRTCIVIAHRLSTIQNADLIVVFQNGRVKEHGTHQQLAQKGIFYSMVSQAGTQNL

>ABC86

MVTVGNYCEAEGPVGPAWMQDGLSPCFPTLVPSTRMALGTALVLALPCRRRERPAGADSLSWGAGPR
 ISPYVQLLLATLQQAALPLAGLAGRVTARGAPLPSYLLSVLESAGACGLWLLVVRSQARQRLAM
 GIWIKFHRSPGLLWTVAFAAENALVSNSPQWWWARADLGQVQPSLWLVRYVVSGLFVLGLWAP
 GLRPOSQTYLQVHEEDQDVRSQVRSAQOSTWRDFGRKLRLSGYLWPRGSPALQLVVLICLGLMGLER
 ALNVLVPFYRNIVNLLTEKAPWNSLAWITVTSVFLKFLOQGGTGSTGFVSNLRTFLWIRVQQFTSRRV
 ELLIFSHLHELSLRWHLRGLRTGEVRLIADRGTSVTTGGLSYLVFNVIPTLADIIGLIYPSMFFNAWFG
 LIVFLCMSSLTLLTIVVTEWRTKFRAMNTQENATRAVADSLNFTETVKYNAESEVERYREAIKY
 QGLEWKSSASVLLNQTQNLVIGLGLLAGSLLCAYFTEQKLQVGDYVLFGTIIQLYMPLNWFGTYR
 MIOTNFIDMENMFDLLEETEVKDLPGAGPLRFQKGRIEFENVHFYSYADGRETLQDVSVFTVMPGQTLAL
 VGPSCAGKSTILRLLPFRFYDISSGCIRIDGQDISQVITQASLRSHIGVVPQDTVLFNDTIADNIRYGRV
 AGNDEVEAAAQAGIHDIAIMAFPEGYRTQVGERGLKLSGGEKQRVAIARTILKAPGIILLDEATSALD
 SNERAIQASLAKCVCANRTTIVVAHRLSTVNVNADQILVIKDGCIVERGRHEALLSRGGVYADMWQLQQQ
 EETSEDTKPQTMER

>ABC87

MALLAHMSWRWAAAAAAPEKRRHSAILIRPLVSVSGSGPQWRPHQLGALGTARAYQIPESLKSITWQRL
 GKGNSGQFLDAAKALQWPLEIKRTCWHGHAGGGLHTDPKEGLKDVDTRKIIKAMLSYVWPKDRLRA
 RVPISLGFLLGAKAMNIVVPMFKYAVDLSNQMSGNMNLSDAPNTVATMATAVILIGYGVSRAGAAPPN
 EVRNAVFGKVAQNSIRRALKNVFLHLHNLDLGFLHSRQTCALSKAIDRGTRGTSFVLSALVFNLPNV
 EVMLLVSGLVLYKCCAQLLGNLGLTGTYTAFTVAVTRWRTRFRLEIDQADNDAGNAIDSLLNYETVKY
 FNNERYEAQRYDGFLKTQYETASLKSSTLAMNFGQSAIFSVGLTAIMVLASQGIVAGTITVGDLMVN
 GLLFQLSLPLNGLGTQYRETQALIDMNTLFTLLKVDTQIKDKVUMASPLQITPQTATVAFDNVHFYIE
 GOKVLSGSISEFVPGAKKVAITVGGSGKSTIVRLFRFYPEPKGSITYLAGQNIQDVSLESLRRAVGVP
 QDAVLPHNTIYNNLLYGNIASPEEVYAVAKLAGLHDAILRMPHGVDTQVGERGLKLSGGEKQRVAIAR
 AILKDPPVILYDEATSSL SITEETILGAMKDVKHRTSIFIARLSTVVADEIIVLDQGKVAERGTH
 HGLLANPHSISYSEMWTQSSRVQNHDNPKWEAKKENISKEEERKKLQEEITVNSVRGCGNCSC

>ABC88

MLVHLFRVGIRGGPFPGRLLPPLRFQTFSAVRYSDGYRSSLLRAVAHLSQLWAHLPRAPLAPRWSPS
 AWCVWGALLCPMVLSKHPLCLVALCEAAEAPPASSPHVVGSRFWKLFNFWQFLPHPLLVLGVAVVLA
 LGAALVNVQIPLLLGQLVKKVVAQYTRDHVGSMTESQNLSTHLLILYGVQGLLTFGYLVLSSHVGERMA
 VDMRMRALFSSLRQNITFEDANKTGQLVSRLTTDVQEKFSSFKLVSQGLRSCSCLVSLSMISTR
 LTLLLMVATPALMGVGTLMGSLRKLSRQCQEHIARAMGVADEALCNVRTVRALAMEOREEERYCAELE
 ACRCRAEELGRGIALFQGLSNIAFNCMVLGTLFIGGSVLAGQQLTGGDMSFLVASQTVQRSMANSLV
 FGQVVRGLSAGARVFEMALNPCIPLSGCCVPKEQLRSVTFQNCVFSYPCRGFPEVLFKDFTLTPPG
 KIVALVGQSGGKTTVASLLERFYDPTAGVVMMDGRDLRTLDPWSLWRQVGVFISQEPVLFGTITIMENI
 RFCKLEASDEEVYTAAREANAHFITSFPEGYNTVVERGTTLSGGQKQRRIATARALIKQPTVILDEA
 TSALDAESERVQEAIDRASAGRTVLLVIAHRLSTVRGAHCIVVMADGRVWEAGTHEELLKKGGYAEI
 RRQALDAPRTAAPPKPKPEGPRSHQHKS

>ABC89

MRLWKAVVVTLAFMSVDICVTTAIIYVSHLDRSLLDIRHFNFDSVLDLWAACLYRSCLLGAATGVA
 KNSALGPRLRASWLVITLVLFCVGIIYAMVKLLFSEVRPPIRDWPFWALFWVWTYISLGSFLWLL
 TVRPGTQALEPGAATEAEGFPGSRPPPEQASGATLQKLLSYTKPDVAFLVAASFFLIVAALGETFLPY
 YTGRAIDGIVIQLKSRLTSDTMVSDLVSQNVFLRNTVKVTGVVVFMPSLWQSLVTFMGFIPIIMMVSN
 FDENRTGDLISRLTSDTMVSDLVSQNVFLRNTVKVTGVVVFMPSLWQSLVTFMGFIPIIMMVSN
 YGKYYKRLSKEVQNALARAATTAETISAMKTVRSPANEAAAEEVYLRKLQVYKLNKEAAAYMMVW
 GSGSGVSVYSGLMQGVAAEKVFIFIDRQPTMVHDGSLAPDHLEGRVDFENVTFTYRTRPHTQVLQNV
 FSLSPGKVTAALVGPSSGSGKSSCVNILENFYPLEGGRVLLDGKPIISAYDHKYLHRVISLVSQEPVLFARS
 ITDNISYGLPTVPEMVVEAAQKANAHGFIIMELQDGYSTETGEKAQLSGGQKQRVAMARALVRNPV
 ILDEATSALDAESEYLIQQAIHGNLQKHTVLIIAHRLSTVHEAHLLIVVLDKGRVVQQGTHQQLAQGGL
 YAKLVQRQMLGLQPAADFTAGHNEPVANGSHKA

>ABC8B10

MRGPPAWPLRLEPPSPAEPGRLLPVACVWAASRVPGSLSPFTGLRPARIWAGPALLWGVAARRWR
 SGCRCGGPGASRGVLGLARLLGLWARGPGSCRGAFAGPCAPRLPRARFPGPAAAAGDEAWRRGPA
 APPGDKGRLRPAAGLPEARLKLGLAYPERRLLAAAVGFLTMSSVISMSPFFLGKIIDVIYTNPTV
 SDNLTRLCLGLSAVFLCGAAANAIRVYLMQTSQGRIVNRRLTLSFSSILRQEVAFFDKTRTGEINRLS
 SDTALLGRSTENLSDGLRAGAQASVGISMFFVSPNLATFVLSVPPVSIIAVIYGRYLRKLTKVTD

Figure 3 - 6

SLAQATQLAERIGNVRTVRAFGKEMTEIEKYASKVDHVNLARKEAVARAGFFGATGLSGNLIVLSVL
 YKGGLLMSAHMTVGELOSSFLMYAFWVGISIGGLSSFYELMKGIGACGRLLWELLEREPKLPFNEGVL
 NEKSFQGALEFKNVHFAYPARPEVPIFQDFSLSPGSVTALVGPGSGKSTVLSLLRLYNPASGTIS
 LDGHDRDQLNPVWLRSKIGTVSQEPILFSCSTAENIAYGADDPSSVTAEEIQRVAEVANAVAFIRNFPQ
 GFNTVVGEKGVLSSGGQKQRIAIARALLKNPKILLDEATSALDAENEYLVQEALDRLMDGRTVILVIAH
 RLSTIKNANMVAVLDQGKITEYGRHEELLSKPNQYRKLNMNKQSFISA

>ABCB11=SPGP= Sister of P-glycoprotein

MSDSVILRSIKKFGEEENDGFESDKSYNNDKSRLQDEKKGDGVRRGVFFQLPRFSSSTDIWLMFVGSLCA
 FLHGIAQPGVLLIFGTMDFIDYDVELQELQIPGKACVNNTIVWTNSLNQNMTNGTRCGLLNIIBSEM
 IKFASYAGIAVAVLITGYIQICFWVIAAARQIQKMRKFYPRIMRMEIGWFDCNSVGEINTRFSDDIN
 KINDAIAQDMALIQRMTSTICCFLLGFRGKLTIVSPLIGIAATIGLSVSKFTDYELKAYAK
 AGVVADEVISMRVTAAGFGEKREVEREYKNLFAQRWGIRKGIVMGFFTFGVWCLIFLCYAVAFWYGS
 TLVLDEGEYTPGTLVQIFLSVIVGALNIGNAPCLEARATGAAATSIFETIDRKPIIDCMSEDGYKLD
 RIKGEIEFHNTFPHYPSRPREVKILNDLNVMVKPGEMTALVGPGSGAKSTALQIQRFYDPCEGMVTDG
 HDIIRSLNIQWLRDQIGITVEQEPUFLFSTTAENIYGRGDEATMEDIQVAKEANAYNFIMDLQQQFDLTLV
 GEGGGCQMSGQKQRVALARALIRNPKILMATSALDNESAEAMVQEVLISKIQHGTISVAHRLSTVR
 AADTILIGFEHGTAVERGTHEELLERKGVYPTLQSQGNQALNEEDIDATEDDMILARTFSRGSYQDS
 LRASIRQRSKSQLSYLVHEPPLAVVHDKSTYEEDRKDKDIPVQEEVEPAVRRILKFAPEWPYMLVGS
 VGAAVNGTVTPLYAFLFSQILGTFSPIDKEEQRSQINGVCLLFVAMGCVSLFTQFLQGYFAKSGELLT
 KRLRKFGFRAMLGQDIWFFDLRNPSGALTTRLATDASQVQGAAGSQIGMIVNSFTNVITVAMILAFSPS
 WKLSLVILCFPLALSQATQTRMLTGFAASRDQKALEMVGQITNEALSIRTVAGIGKERRFIEALETE
 LEKPKFKTAIQKANIYGFCAFAQCMFIANSASYRYGGYLISNEGLHFSYVFRVISAVVLSATALGRAF
 SYTPSYAKAKISAARRFQQLDRQPPISVYNTAGEKWDNFQGKIDFVDCFKTYPSPRDPDSQVLNGLSVSIS
 PGQTЛАFVGSGCGKSTSQIQLLERFYDPDQGKVMDGHDSSKVNQFLRSNIGIVSQEPVLFACSIMDN
 IKYGDNTKEIPMERVIAAKQAOLHDFVMSLPEKYEITNVGSQGSQSLSRGEKQRIAIARAIVRDPKILL
 DEATSALDTESEKTVQVALDKAREGRTCIVIAHRLSTIQNADIIAVMAQGVVIEKGTHEELMAQKGAYY
 KLVTTGSPIS

>ABCC1=MRP1= multidrug resistance associated protein 1

MALRGFCSDGSDPLWDWNVWNTSNPDFTKCFQNTVLLWVPCFYLWACFPYFLYLSRHDRGYIQMTP
 LNKTKTALGFLWIVCWADLFYFSWBRSRGIFLAPVFLVSPTLLGITTLLATFLIQLERRKGVOSSGIM
 LTFWLVALVCALAILRSKIMTALKEDAQVDFRBDITFYVYFSLLLIQLVLSCSFSDRSPLFSETIHDPNP
 CPESSASFSLSRITFWWTGTLIVRGYRQPLEGSDLWSLNKEDTSEQVVPVLVKNWKKECAKTRKQPVKV
 YSSKDPAQPKESSKVDAANEVEALIVKSPQKEWNPSSLFKVLYKTFGPYFLMSFFKAIHDLMMFSGPQI
 LKLLIKFVNDTAKPDWQGYFTVLLFVACLQLTQLVHLQYFHCFCVSGMRICTAVIGAVYRKALVITNSA
 RKSSTVGEVNLMSVDAQRFMDLATYINIWSAQLQVILALYLLWLNLPGSVLAGVAVMVLMPVNAVM
 AMKTKTYQVAHMKSDNRKLMNEILNGIKVLKLYAWELAFDKVLAIRQEEKLVLLKSAAYSAGVFT
 WVCCTPFLASVSLKRLRIFLSSHEELEPDSIERRPVKDGGGNTSITVRNATFTIWARSDDPPTLNGITFSIPE
 GALVAVVQGVCGKSSLSALLAEMDKVGEHVIAKGSVAYVPQOAWIQNDSLRENILFGCOLEEPYYRS
 VIQACALLPDLEILPSGDRTEIGEKVNLSSGGQKQRVSLARAVYNSADIYLFDPLSAVDAHVGKHIFE
 NVIGPKGMLKNKTRILVTHSMSYLPQDVVIIVMSGKISEMGSYOELLARDGFAEFLRTYASTEQEQQD
 AEENGVTGVSGPGKEAKQMENGMLVTDACKQLQRQLSSSSSYSGDISRHHNSTAELOQKAEEAKKEETWK
 LMEADKAQTQCVKLSVWYDMKAIGLPIFSLSIPLFCMCNHVSALASNYWLSLWTDPPIVNGTQEHTKVR
 LSVYGALGISQGIAVPGYMSMAVSIGGLASRLCLHVDLHSILRSPMSFFERTPSGNLVRNFSKELDTVD
 SMIPEVIKMFGSLFNVIGACIVLATTIAIIIPPLGLIYFVQRPYVASSRQLKRLESVSRSPVYS
 HFNETLLGVSVIRAFEEQERFIHQSDLKVDENQKAYPSIVANRVLAVRLECVNCIVLPAALFAVISR
 HSLASAGLVLGSVSYSLQVTTYLNWLVRLMSSEMETNIVAVERLKEYSETEKEAPWQIQTAPPSSWPQVG
 RVEFRNYCLYREDDFVLRHINVTINGCEKVGIVGTGAGKSSLTLGLFRINESAEGEI IIDGINTIAKI
 GLHDLRFKITIIPQDPVLFSGSLRMNLDLPSQYSDEEWTSLELAHLKDFVSLPDKLDHECAEGGENL
 SVGQRQLVCLARALLRKTKILVLD**EATAAVDLETDDLIQSTIRTQFEDCTVLTIAHRLNTIMDYTRVIV**
 LDKGEIQBEYAPSDLLQQRGLFYSMAKDAGLV

>ABCC2=MRP2= Multi Drug Resistance Associated Protein 2

MLEKFCNSTFWNSSFLDSPEADPLLCFEQTVLWVILPLGLFLWLLAPWQLLHVYKSRTKRSSTTKLYLAKQ
 VFVGFLLILAAIELALVLTEDSGQATVPAVRYTNPSLYLGTWLLVLLIQYSROWCVQKNSWFLSLFWIL
 SILCGTFQFQTLIRTLQGDNSNLAYSCLFFISYGFQILILIFSASENNESSNNPSSIASFLLSITYS
 WYDSIILKGYKRPLTLEDWVVEDEEMKTKLVSFKFET:MKRELQKARRALQRRQEKSQQNSGARLPGL
 NKNQSOSQDALVLEDVEKKKKSGTKKDVPKSWLMLKFKTFYMWLLKSFLKLVNDIFTFVSPQLLKL
 LISFASDRDTYLWIGYLCAILFTAALIQSFCCLQCYFQLCFKLGKVVRTAIMASVYKKALTLSMLARKE
 YTGETVNLMSVDAQKLMVTNFMHMLWSSVLTIVLSEFFLWRLEGPSVLAGVGVMLVIPINAILSTK
 SKTIQVKNMKNKDRKLKIMNEILSGIKLKYFAWEPSFRDQVQNLRKKEKLKNLAFSQLQCVVIFVFQL
 TPVLVSVVTFSVVVLVDSNNILDAQKAFTSITLFNILRPLSMLPMIISMLQASVSTERLEKYLGGDD
 LDTSAIRHDCNFDKAMQFSEASFTWEHDSEATVRDVNLIDIMAGQLVAVIGPGVGCKSSLISAMLGEMEN
 VHGHITIKGTTAYVPQQSWIQQNGTIKDNILFGTEFNEKRYQQVLEACALLPDLEMPLPGGDLAEIGEKGI
 NLGGQKQKRIISLARATYQNLDIYLLDDPLSAVDAHVGKHIIFNKVLPNGLKGKTRLLVTHSMHFLPQV

Figure 3 - 7

DEIVVILGNNTIVEKGYSALLAKGEFAKNLKTFLRHTGPEEEATVHDGSEEDDYGLISSVEEIPED
 ASITMRRENSFRRTLSRSRSNGRHLKSLRNSLKTRNVNSLKEDEELVKQGKLIKKEFIELTKVKFSI
 YLEYLQAIGLGSIFIIIAFLAVMNSVAFTGNSLWLSAFTSDSKIFNSTDYDASQRDMRVGVYGAFLGAOG
 IFVFIAHFWSAGFGVHASNLHQNLLNIRAPMRFFDTPTGRIVNRFAGDISTVDDTLPSLRSWIT
 CPLGIISTLVMICMATPVFTIIVIPLGIIVSVMFVTSRQLRRLDSTVRSPIYSHFSETVSLPVI
 RAFEHQQRFLKHNEVRIDTNQKCVPSWITSNRLAIRELVLGNLTFFSALMMVYRDTLSGDTVGFL
 SNALNITQTLNWLVRLVMTSEIETNIVAFERITEYTAKVENEAPWVTDKRPPWDPSKGKIQFNNYQVRYRP
 ELDLVLRCITCDIGSMKIGVVGRGAKSSLTNCFLRILEAAGGQIITDGVDIASIGLHDLREKLTI
 PQDPILPSGSRLMNLDPEEDEIWKALELAHLKSFVASLQLGLSHEVTEAGGNLSIGQRQLCLGR
 ALLRKSKILVLDDEATAAVDLETDNLIQTITQNEFAHCTVITIAHRLHTIMDSDKVMVLNGKIECGSP
 EELLQIPGPFYFMAKEAGIENVNSTKF

>ABCC3=MRP3= Multi Drug Resistance Associated Protein 3

MDALCGSGELGSKFWDNSLNVHTENPDLPDTPCFQNSLLAWVPCIYLWVALPCYLLYLRHHCRGYIILSHL
 SKLKMVLGVLWLVCWSWADLFYSPFHGLVHGRAPAVPFVTPLVVGVMLLATLLIQYERLQGVQSSGVLI
 IFWFLCVVCAIIVPFRSKILLAKAEGEIISDPFRPTFYIHFAVLVSALILACFREKPPFSAKNVDPNPY
 PETSAFLSRLFFWWPTKMAIYGYRHPLEEKDLWLSKEEDRSQMVQQLLEAWRKQEQKQTARHKASAAP
 GKNASGEDEVLLGARPRPKPSFLKALLATFGSSFLISACFKLQIQLQFSPINPQLSILIRFISNPMP
 SWWGFVLVAGLMFLCSMMQSLILQHYYHYIPVTGVKFRTGIMGVIYRKALVITNSVKRASTVGEIVNLM
 VDAQRFMDDLPFLNLLWSAPIQIILAIYFLWQNLCGPSLAGVAFMVLITPLNGAVAVKMRFCVQKQMKL
 KDSRIKLMSEILNGIKVLKLYAWEPSFLKQVEGIRQGEQQLLRTAAYLHTTTFTWMCSPFLVTLITLW
 VVYVDPNVLDAEKAFVSVSLFNLRLPLNMLPQLISNLQTQASVSLKRIQQFLSQEELDPQSVERKTI
 SPGYAITTHSGTFITWAQDLPPLTLEGSLDIQVPGALVAVVGPVCGKSSLVSALLGEMEKGKLVHMKGS
 VAYVPQQAQIQCNTLQENVLFGKALNPKRYQQTLEACALLADLEMPLPGGDQTEIGEKGINLSGGQRQRV
 SLARAVYSDADIFLDDPLSAVDSHVAKHIFDHVIGPEGVLACKTRVLVTHGISFLPQTDFTIILVADGQ
 VSEMGPYPALLQRNGSPANFLCNYAPDEDQGHLEDSWTALEGAEDKEALLIEDTLSNHTDLTDNDPVTY
 VVQKQFMRQLSALSSDGEGQGRPVPRRHLGPSEKVQVTEAKADALTQEKEKAAGTVELSVFWDYAKAV
 GLCTTLAICLLYVGQSAAIAGANWLSAWNTNDAMADSRQNNTSLRGVYALGILQGFLVMLAAMAMAA
 CGIQAARVILQALLHNKIRPSQSFFDTTSPGRILNCFSKDIYVVDVLEAPVILMLNSFFNAISTLVVI
 MASTPLFTVILPLAVLYTTLVQRFYATTSRQLKLESRSPIYSHFSETVIGASVIRAYNRSRDFEII
 SDTKVDANQRSCPYLIISNRWLSIGVEFGNCVVLFAALFAVIGRSSLNPGVLVGLSVSYSLQVTALNW
 MIRMMMSDLESNIVAVERKEYSKTETEAPWVVEGSRPEGWPVPRGEVEFRNYSVRYRPGGLDVLIRDLSL
 HVHGKEVGIVGRTGAGKSSMTLCLFRILEAIDGNGRNVAIDGLHDLRSQTLIIPQDPILPSGTL
 RMNLDPFGSYSEEDIWKAELSHLHTFVSSQAGLDQFCSEGGENLSVGQRQLVCLARALLRKSRILVL
 DEATAAIDLETDNLIQATIRTQFDTCVLTIAHRLNTIMDYTRVLVLDKGVVAEPDSPANLIAARGIFY
 GMARDAGLA

>ABCC4= MRP4= Multidrug Resistance Associated Protein 4

MLPVYQEVKPNPLQDANICSRVFFWWLNPFLKIGHKRLEEDDMYSVLPEDRSQHLGEELQGFWDKEVL
 RAENDAQKPSSLTRAIICKYWKSYLVLGIFTLIEESAKVIQPIFLGKIIINYFENYDPMDSVALNTAYAYA
 TVLTFTCLLTLATLHYYHVOCAGMRLRVAMCHMITYRKALRSLNMAMGKTTTGQIVNLLSNDVNKFDQ
 VTVFLHFLWAGPLQIAITVTLFFPSAIERVSEAIIVSIRRIQTFLLDEISQRNRQLPSDGKMMHVQD
 NEVITGIRIKMYAWEKSNSLITNLRKEISKILRSSLRGMNLSAFFSASKIIVEVTFTTYVLLGSV
 ITASRVFVAVTLYGAVRLITVTLFFPSAIERVSEAIIVSIRRIQTFLLDEISQRNRQLPSDGKMMHVQD
 FTAFWDKASEPTPLQGLSFTVRPGELLAUVVPGVAGKSSLLSAVLGELAPSGLVSVHGRAYVSQQPW
 VFSGTLRSNLFKGKKYKEVYEVKVIKACALKKDQLLEDGDTLVICDRGTTLSGGQKARVNLRARAVYQD
 ADIYLLDDPLSAVDAEVSRHLFCICLQILHEKITILVTHQLQYKLAQSQILILKDGMVQKGTTEFL
 KSGIDFGSLLKKDNEESEQPPVPGPTPLRNRTFSESSVWSQSSRPSLKDGALESQDTEENVPTVTLSEEN
 RSEGKVGQAYKNYFRAGAHWIVFIFILLNTAAQVAYVLQDWLWSYWANKQSMLNVTNGGNVTEKL
 DLNWYLGISGLTVATVLFGIAERSLLVFYLVNSSQTLHNKMFESTILKAPVLFDRNPIGRILNRSKD
 IGHLLDDPLTFLDFIQLLQQVGVSVAVAVIPWIAIPVPLGIIIFLRRYFLETSRDVKRLESTR
 SPVFSHLSSSLQGLWTIRAKAERCQELDAHQLHSEAWFLFTTSRWFVRLDAICAMFVIIIVAFG
 SLLIATKLDAGQVGLALSYALITLGMFMQWCVRQSAEVENMISVERIYEYDLEKEAPWEYQKRPPPAW
 PHEGVIIIFDNVNFMYSPGGPLVVKHLLTALIKSQEKVGIVGRGAGKSSLISALFRLSEPEGIWIDKIL
 TTEIGLHDLRKKMSIIPQEPVLFGTGMRKNLDPFKEHTDEELWNALQEVQLKETIEDLPGKMDTELAES
 GSNEFVGQRQLVCLARAILRKQNLIIIDEATANVDPRTDELIQKKIREKFAHCTVLTIAHRLNTIIDSD
 KIMVLDSCRLKEYDEPYVLLQNKESLFYKMWQQLGKAEEAALTETAKQVYFKRNYPHIGHTDMMVNTNS
 NGQPSTLTIFETAL

>ABCC5= MRP5= Multidrug Resistance Associated Protein 5

MKDIDIGKEYIIPSPGYRSVRERTSTSSTGTHRDREDSKFRRTRPLECQDALEAAEGLSLDASMHSQ
 RILDEEHPKGKYHHGLSALKPIRTTSKQHHPVDNAGLFSCMTFSWLSSLRVAKKKGELSMDUWSLSK
 HESSDVNCRRLERLWQEEELNEVGPDAAISLRRVVWIFCRTLILSIVCLMITQLAGFSGPAPMVKHLLEY
 TQATESNLQYSLLLVLGLLTLTEIVRWSLALTWALNVRTGVRGAILTMFKKILKLKNIKEKSLGEL
 INICSNNDQRMFEAAAVGSLLAGGPVAILGMIVNVIILGPTGFLGSASFILFYPAMMFASRLTAYFRR
 KCVAATDERVQKMNEVLTYIKFIKMYAWVKA=SOSVQKIREEEERRILEKAGYFQGIVTVGVAPIVVVIAS

Figure 3 - 8

VVTFSVHMTLGFDLTAAQAFVTVTFVNSTMTPALKVTPFSVKSLSSEAVDRFKSIFLMEEVHMICKNP
 ASPHIKIEMKNATLAWDSSHSSIQNSPKLTPKMKDKRASRGKKEVKVQLQRTEHQAVLAEQKGHLLLD
 SDERPSPEEEGKHILHGHLRLQRQLHSIDLEIQEGLVIGICSGVGSKTSLISAILGQMTLLEGSTIAI
 SGTFAYVAQQAWILNATLRDNILFGKEYDEERYNSVLNSCLRPDLAIPSSDLTEIGERGANLSCGQR
 QRIISLARALYSDRSIYILDPPSALDAHVNHFNSAIRKHLKSKTFLVTHQLQYLVDCDEVIFMKEG
 CITERGTHEELMNLNQDYATIFNNLLGETPPVINSKKETSGSQKKSQDKGPKGTVKEAKVPEEG
 QLVQLEEKQGSVPWSVYGVYIQAAGGPLAFLVIMALFMLNVGSTAFSTWLSYWKQGSGNTTVRGN
 ETSVSDSMKDNPBMQYYASIYALSMAVMLLKAIARGVVFVKGTLRASSRLHDELFRRIILRSPMFFDTT
 PTGRILNRFSKDMEDVDRPLPFQAEMLIQNVLVFFCVMGLAGVFPWLVAVGPLVILFSVLHIVSRVL
 IRELKRLDNITQSPPLSHITSSIQGLATIHAYNKGQELFLHRYQELLDNQAPFFLFTCAMRWLAVRLDL
 ISIALTTTGLMIVLMLHGQIPPAYLAGISAYVLTGLFQFTVRLASETEARFTSVERINHYIKTLSLE
 APARIKNKAPSNDPWPQEGETFENAEEMYRENLPVLLKVSFTIKPKERIGIVGRGTSGGKSSLGMALFR
 LVELSGGCIKIDGVRISDIGLADLRSKLIIPQEPVLFSGTVRSNLDPFNQYTEDQIWDAERTHMKEC
 IAQLPLKLESEVMENGDNFSVGERQLLCIARALLRHCKILILDEATAAMDTETDLLIQLQETIREAFADCT
 MTLIAHRLHTVLGSDRIMVLAQGQVVEFDTPSVLLSNDDSSRFYAMFAAAENKVAVKG

>ABCC6= MRP6= Multidrug Resistance Associated Protein 6

MAAPAEPCAGQGVWNQTEPEPAAATSLSLCFLR TAGWVPPMLWVLGPIYLLFIHHGRGYLWMSPLF
 KAKMVLGFALIVLCTSSVAVALWKIQQGTPPEAPEFLIFIPTVWLTMSFAVFLINTERKGVQSSGVLF
 YWLLCFCPATNAAQASGAGFQSDFPVRLSTYLCLSLLVVAQFVLSCLADQPPFFPEDPQQSNPCPETG
 AAFPSKATFWWVSGLVWRGYRRPLRKPDWLSSLRENSSEELVSRLEKEWMRNRSAARRHNKAIAFPKRKG
 GSGMKAPETEPFRLQEGSQWRPLLKAIWQVFHSTFLGTLSLIISDVFRFTVPLKLLSLFLEFIGDPKPP
 AWKGYLLAVLMLFLSACLQTLFEQQNMYRLKVLQMRLRSAITGLVYRKVLALSSGSRKASAVGDVVNLVS
 VDVQRRLTESVLYNGLWLPLVWVIVCFVYLWQLLGPSALTIAVFLSLLPLNFFTISKRRNHHQEEQMRQ
 KDSRARLRTSLRNSKTIKFHWGEAFGLDRVLRGIRGQELGALRTSGLFSVLSFQVSTFLVALVVFA
 VHTLVAENAMNAEKAFTLTVLNLNKAQAFPLPSIHSVLSVQARVSFDRLVTFLCLEEVDPGVVDSSSG
 SAAGKDCITIHSATFAWSQESPPCLHRINLTVPQGCLLA VVPGVAGKSSLLSALLGELSKEVGFVSI
 GAVAYVPQEA WVNQNTSVENVCFGQELDPWLERVL EACALQPDVDSFPEGIHTSIGEQGMNLSSGQKQ
 RLSLARAVYRKAAVYLLDPLAADDLDAHVGQHVFNQVIGPGGLLQGTTRILVTHALHILPQADWITVLAN
 GAIAMEGYSQELLQRKGALVCLLDQARQPGDRGEGETEPGTSTKDPRTGSAGRPELRRERSIKSVPEK
 DRTTSEAQTVEPLDDPDRAGWPAKGDSDIYQGRVKATVHLAYLRAVGTPLCLYALFLFCQOVAFCRGY
 WLSLWADDPAVGGQQTAALRGGIFGLLGCLQAGLFASMAVLLGARASRLLFQRLLWDVVRSPISF
 FERTPIGHNLNRFSKETDITVDIIPDKLRSLLMYAFGLLEVSLSVVAVATPLATVAILPLFLLYAGFQSL
 YVSSCQLRRLLESASYSSVCSHMAETFGSTVVRAFRTOQFVAQNNARVDESQRI SFPRLVADRWLAA
 NVELLNGNGLVFAAATCAVLSKAHLSACLQGFSVSAALQVTTQTLQWVVRNTDLENSIVSVERMQDYAWT
 PKEAPWRLPTCAAQPPWPGGGQIEFRDFGLRYRPELPLAVQGVSFSKIHAGEKVGVGRTGAGKSSLASG
 LLRLQEEAAEGGIWIDGVPIAHVGLHTLRSRISIIPQDPILFPGSLRMNLDLQEHSDDEAIWAALETVQL
 KALVASLPGCQLOYKCADRGEDLSVGQKQLLCLARALLRKTQILILDEATAAVDPGTELQMQAMLGSWFA
 OCTVLLIAHRLRSVMDCARLVMDKGQVAESGSPAQLLAQKGLFYRLAQESGLV

>ABCC7= cystic fibrosis transmembrane conductance regulator

MORSPLEAKSVSKLFFSWTRPILRKYQRLELSDIYQIPSVDSDANLSEKLEREWDRRELASKKNPKL
 INALRRCCFFWRMFYGIYFLGEVTKAQPLLLGRIIASYDPMKERSIAIYLGLCLLFIVRTLLL
 HPAIFGLHHIGMOMRIAMFSKTYKKTLLKLSRVLKDQISGQLVSLLSNNLNKFDDEGLALAHFWIAPLQ
 VALLMGLIWEQASAFCGLGFLIVLALFQAGLGRMMMKYRDQRAKGKISERLVTSEMIENIQSVKAYC
 WEEAMEKMIENLRQTELKLTRKAAYVRYFNSSAFFSGFVVFLSVPYALIKGILRKIFTTISFCIV
 LRMAVTQFPAWVQTYDLSGAINKIQDFLQKQEYKTEYNLTTEVVMENUTAFWEEGFELFEKAKQ
 NNNNRKTTSNDDSLFFSNPSLLGTPVLDKINPFIERGQQLAVAGSTGAGKTSSLMMIMGELEPSEGKIK
 HSGRISFCFSQFSWIMPGTKEIIFGVSYDEYRYSVIAKACQLEEDISKFAEKDNIVLGEGGITTLSGGQ
 RARI SLARAVYKDADLYLIDSPFPGYLDVLTKEIFESCVCVCKLMANKTRILVTSKMEHLKKADKILILHE
 GSYYFYGTFSQNLQPDFSSKLMGCDSDQFSAAERRNSILTELHRSLEGDAPSVWTETKKQSFQKT
 GEFGEKRNSILNPNISRKFISIVQKTPQYNGIEEDSDEPLERRISLVPDSEOEAIPLRISVISTGP
 TLQARRRQSVNLNMTHSVNQGQNIHRKTTASTRKVSLAPQANLTTELIDSRRRLSQTGLEISEEINEED
 LKECFFDDMESTPAVTTWNTLYRJITVHKSLIFVLIWLVIFLAEVAAASLVLWLLGNTPLQDKGNSTH
 SRNNSYAVIITSTSSYYVFYIYVGVADTLLAMGFFRGLPLVHTLITVSKILHHKMLHSQLPAMSTLNT
 LKAGGILNRFNSKDIAILDILPLTIFDFIQLLLIVIGAIAVVAVLQPYIFVATVPIVAFIMLRAYFLQ
 TSQQLKQLESEGRSPIFTLVTSLKGLWTLRAFGRQPYFETLFHKAHLNHTANWFLYLSLRLWFOMRIE
 MIFVIFFIAVTFISIILTTGEGEGRVGIELTLAMNIMSTLQWAVNSSLVDVDSLRSVSRVFKFIDMPTEG
 KPTKSTKPYKNCOLSKVMIIENSHVKKDDIWPSGGQMTVKDLTAKYEGGNALIENISFSISPGQRVGL
 LGRTGSGKSTLSSAFLRLLNTEGEIQIDGVWSDSITLQQWRKAFGVIQKVFIFSGTFRKNLDPEQWS
 DQEIWKVADEVGLRSVIEQFFGKLDLDFVLVDGCCVLSHGHKQLMCLARSVLSKAKILLDEPSAHDLPVT
 YQII RRTLKQAFADCTVILCEHRIEAMLECCQFLVTEENKVRQYDSIQKLLNERSLFRQATSPSDRVKL
 FPHRNSSKCKSKPQIAALKETEEEVQDTRL

>ABCC8=SUR1=Sulfonurea Receptor 1

Figure 3 - 9

MPLAFCGSENHSAAYRVDQGVLNNGCFVDALNVPHVFLLFITFPILFIGWGSQSSKVIIHHSTWLHFP
 GHNLWRILTFMLLFVLC2IAEGILSDGVTESHHLHYMPAGMAVTSSVYHNIETSNFPKLLIA
 LLVYWTLAFITKTICKFVKLLDHALGFSQLRCFTGLVILYGMLLVEVNVRVRRYIFFKTPREVKPP
 EDLQDLGVRFQLPFVNLPSPKGTYWMNAFIKTAHKKPIDLRAIGKPIVMRALTNYQRLCEAFDAQVRK
 DIQGTQGARAIWQALSHAFGRRLVLSSTFRILADLLGPAGPLCIFGIVDHLGKENDVFQPKTQFLGVYF
 VSSQEFLANAYVLAVLLFLALLQRTFLQASYYVAIETGINLRGAIQTKLYNKIMILSTSNSLMSGEMTA
 GQICNLVAIDTNQLMWFFLCPNLWAMPQIIVGVILLYILGVSAVIAVILLAPVQYFVATKLSQ
 AQRSTLEYSNERLKQTNEMLRGIKLLKLYAWENIFRTRVETTRRKEMTSLSRAFAITYTSISIFMNTAIP
 AAVLITFVGHSVPSKEADFSPSVAFASLFTLVTPLSSVRSVTKALSVQKLSEFLSSAEIRE
 EQCAPHEPTPQGPASKYQAVPLRVNVRKRPAREDCRGLTGPLQSLVPSPADGDADNCCVQIMGGFTWTP
 DGIPILSNITIRIPRGQLTIVGQVCGKSSLLAALGEMQKVSGAVFWSSLPDSEIGEDPSPERETAT
 DLDIIRKRGPVAYAQSKPWLNNATVEENIIFESPFNKQRYKVMIEACSLQPDIDILPHGDQTQIGERGIN
 LSGGQQRORISVARALYOHANVVFLDDPF~~SALDI~~HLSDHLMQAGILELLRDKRTVVLVTHKLQYLPHAD
 WIJAMDGDTIQCREGTLKDFQRSECQLEHWKTMNMRQDQELEKETVERKEPPQGCSRAMSSRDGLL
 QDEEEEEEAEASEEDDNLSMMLHQRAEIPWRACAKYLSAGI~~L~~LLSLLVFSQLLKHMLVVAIDYWLAK
 WTDSALTLPAAARNCSLSQESTLDDQTVYAMVFTVLC~~SLG~~IVCLVTSVTVETGLKVAKRLHRSLLNRI
 ILAPMRFFFETTPLGSILNRFSSDCNTIDQHIPSTLECLSRSRSTLLCVSALAVISYVTPVFLVALLPLAVV
 CYFIQKVFRVAVSRDQLD~~T~~TQLPLL~~S~~HFAETV~~E~~GLTTIRAFRYEARFQQLLEYTDNNIASLFLTA
 ANRWLEVRMEYIGACVVLIAAVTSISNLSHRELSAGLVGLGTYALMVSNYLNWVMVRNLADMELOLGAV
 KRIHGLLKTEAESYEGLLAPS~~I~~PKNWDQGKIQ~~T~~QNLNSVRYDSSLKPVLKHNVALISPQKIGICGRT
 GSGKSSFSLAFFRMVDTFEGHIIIDGIDIRKLP~~L~~HTLPSRLSIILQDPVLFSGTIRFNLDPERKCSDEST
 LWEALEIAQLKLVVKALPGGLDAIITEGGENFSQGQRQLFCLARAFVRKTSIFIMDEATASIDMATENI
 LQKVVMTAFADRTVVTIAHRVHTILSADLVLRGAILEFDKPEKLLSRKDSVASFVRADK

>ABCC9= SUR2= Sulfonurea Receptor 2
 MSLSCFGNNISSYNINDGVLQNSCFVDALNLVPHVFLLFITFPILFIGWGSQSSKVIIHHNTWLHFPGH
 NLRWILTPALLFVHVCE2IAEGIVSDSRESRHLHLPMAVNGFVATTTSIVYYHNIETSNFPKLLALF
 LYWWMAFITKTIKLVKYCQSGLDISNLRCITGMVVI~~N~~GLIMAVEINIVRVRVYFFMNPQKVPPED
 LQDLGVRFQLPFVNLLSKATYWMNTL~~I~~ISAHKKPIDLKAIGKPIVMA~~R~~RTVNYVCLKDAYEEQKKVA
 DHPNRRTPSIWAMYAFGRCPILLSS~~T~~FRLADLLGPAGPLCISGIVQVRVNETQNGTNNTTGISET~~L~~SSK
 EFLENAYVLAVLLFLALI~~L~~QRTFLQASYYV~~T~~IE~~T~~GINLRGALLAMIY~~N~~KILRLSTSNSLMSGEMTLGQIN
 NLVAIETNQLMWFLPLCPNLWAMPQIIMGVILLYNLLGSSALVGA~~A~~VIVLLAPIQYFIATKLAEAQKS
 TLDYSTERLKKTNEILGIKIKLLKLYAWEHI~~C~~CKSVEBTRMKELSS~~T~~FTALY~~T~~TSLSIFMNAAIEIAAVL
 ATFVTHAYASGNNLK~~A~~EEAFA~~S~~LSLPHILVTPLSLL~~S~~FTVVRFAVKAII~~S~~VQKLNE~~P~~LLSDEIGDDSWRT
 GESSLPFESCKKHTGVQPKTINRKQ~~G~~RYHLD~~S~~YEQ~~S~~TRRLPAETEDIA~~I~~KV~~T~~NGYFSG~~G~~SLATLSN
 IDIRIPTGQLTMIVGQVCGKSSLLA~~L~~GE~~M~~Q~~T~~LEGKVHSNVNE~~S~~PEATRSRNRYSVAYAAQK~~P~~
 WLLNAT~~V~~ENITFGSPFNKQRYKAVTDACSLQPDIDLLPFGDQTEIGERGINLSGGQRQRICVARALYQ
 NTNIVFLDDPF~~SALDI~~HLSDHLMQEGILKFLQDDKRTLVLVTHKLQYLTHDWI~~I~~AMKDGSVLRE~~G~~TLK
 DIQTKD~~V~~EYEHWKTLMN~~R~~QDQELEKDM~~A~~DQ~~T~~TLERK~~T~~LR~~A~~MSREAKAQM~~E~~DEDEEEEEEDED~~N~~
 MSTVMRLRTKMPWKTCWRYLTSGGF~~L~~ILM~~I~~FSKLLKHSV~~I~~VAIDYWLAT~~W~~SE~~S~~INNTGADQ~~T~~YY
 VAGFSILC~~G~~AGIFLCLVTS~~T~~VEWMGLTA~~A~~KNLHHN~~L~~NKII~~I~~LG~~P~~IRFFDTPLGL~~L~~LNRF~~S~~AD~~T~~NIID
 QHIPPTLES~~T~~RL~~S~~LLC~~S~~AI~~G~~M~~I~~YATPVFL~~P~~LG~~V~~AFY~~F~~IQ~~K~~Y~~V~~FR~~A~~SK~~D~~LQ~~E~~DD~~S~~TO~~P~~LLC
 HFSETAEG~~L~~TTIRAFRHETRFKQ~~R~~MLE~~T~~DNNIAYFL~~S~~LSAANRW~~E~~VRTDYL~~G~~ACIVLTAS~~S~~IS~~G~~S
 SNSGLVGLCLLYALT~~T~~IN~~Y~~LN~~W~~VRNLAD~~L~~EVQMGAV~~K~~V~~V~~N~~S~~LT~~M~~SE~~N~~Y~~E~~GTMDPSQV~~P~~EW~~W~~Q~~E~~GE
 I~~K~~IHDLCVRYENN~~L~~KPV~~L~~KH~~V~~KAYIKPGQKV~~G~~IC~~G~~RT~~G~~SG~~K~~SS~~L~~AFFRMV~~D~~IFDG~~K~~I~~V~~IDG~~I~~D~~K~~
 PL~~H~~TL~~R~~SR~~L~~SI~~I~~ILQDP~~I~~LS~~G~~S~~I~~RFNLD~~P~~EC~~K~~CT~~D~~DR~~L~~WEA~~L~~A~~Q~~LN~~M~~V~~K~~SL~~P~~GG~~L~~DA~~V~~V~~T~~EG~~E~~NF
 SVGQRQLFCLARAFVRKSSILIMDEATASIDMATENI~~Q~~KV~~V~~MTAFADRTVVTMAHRV~~S~~IM~~D~~AGLV~~V~~
 FSEGILVECDTVPNLFA~~H~~KNGPF~~S~~TLV~~M~~TK

>ABCC10 (partial sequence)
 GSGC~~G~~LA~~K~~REGKNR~~W~~Q~~E~~ASMERLLA~~Q~~LCGSSAAW~~L~~PL~~W~~EGDT~~T~~GHCF~~T~~QLV~~L~~SL~~P~~HALLA~~V~~L~~S~~
 YLGTPRSPDYI~~L~~PCSPGW~~R~~RLA~~A~~SF~~L~~LSV~~P~~LL~~D~~LP~~V~~AL~~P~~PGAG~~P~~G~~P~~IGLE~~V~~LAGC~~V~~AAV~~A~~W~~I~~SH~~S~~
 ALWVLA~~H~~SPHGHSGR~~G~~PLALALV~~A~~LLP~~A~~PA~~V~~L~~V~~TL~~W~~H~~C~~Q~~R~~G~~T~~LL~~F~~PL~~P~~PG~~M~~AR~~C~~L~~L~~L~~I~~Q~~L~~A~~A~~LLAYA
 LGWAAP~~G~~GP~~R~~PRE~~W~~Q~~E~~PL~~L~~P~~E~~Q~~E~~PE~~V~~A~~E~~GES~~W~~LS~~R~~FS~~Y~~AW~~L~~AP~~L~~ARG~~A~~C~~G~~EL~~R~~QP~~Q~~D~~I~~C~~R~~L~~P~~H~~R~~Q~~L~~
 PT~~Y~~LA~~R~~V~~F~~QAH~~W~~Q~~E~~GA~~R~~LR~~W~~AL~~Y~~GA~~F~~GR~~C~~Y~~L~~AL~~G~~~~L~~KL~~V~~GT~~M~~LG~~F~~SG~~P~~LL~~S~~LL~~V~~GF~~L~~EE~~G~~Q~~E~~PL~~H~~GL~~L~~
 LYALGLAGGA~~G~~VL~~G~~AV~~L~~QN~~Q~~Y~~G~~Y~~E~~Y~~K~~V~~T~~Q~~A~~RG~~A~~V~~L~~LY~~C~~AK~~Q~~LG~~P~~SR~~P~~PT~~G~~EA~~N~~LL~~G~~T~~S~~ER~~L~~LN
 F~~A~~GS~~F~~HEA~~W~~GL~~P~~PL~~Q~~LA~~I~~TL~~L~~LYQQGV~~A~~F~~V~~GG~~L~~IL~~A~~LL~~L~~V~~P~~V~~N~~K~~V~~IA~~T~~RI~~M~~AS~~Q~~EM~~L~~Q~~H~~K~~D~~AR~~V~~KL~~V~~
 TELL~~S~~GI~~R~~VI~~K~~FC~~G~~WE~~Q~~AL~~G~~AR~~V~~E~~A~~CR~~A~~REL~~G~~RL~~V~~IKY~~L~~DA~~A~~C~~V~~Y~~W~~AL~~P~~V~~V~~IS~~I~~VI~~F~~Y~~V~~LM~~G~~Q~~L~~
 L~~I~~AT~~K~~V~~F~~T~~A~~L~~L~~VR~~M~~IL~~P~~NN~~F~~P~~W~~VI~~N~~GLEAK~~V~~SL~~D~~RI~~I~~QL~~F~~DL~~P~~N~~H~~N~~P~~Q~~A~~Y~~S~~P~~D~~PP~~A~~E~~P~~ST~~V~~LE~~L~~
 HG~~A~~LF~~S~~W~~D~~P~~V~~G~~T~~S~~L~~ET~~F~~IS~~H~~LEV~~K~~KG~~M~~LV~~G~~IV~~G~~K~~V~~GC~~G~~KS~~L~~AA~~I~~AGE~~L~~HL~~R~~LR~~G~~HA~~V~~VR~~G~~LS~~K~~GF~~G~~LA~~A~~
 TO~~Q~~EP~~W~~I~~Q~~F~~A~~T~~I~~RD~~N~~IF~~G~~KT~~F~~DA~~Q~~LY~~K~~VE~~C~~AL~~N~~DD~~L~~S~~I~~LP~~A~~CG~~D~~Q~~T~~EV~~G~~KG~~V~~TL~~S~~GG~~Q~~R~~A~~T~~A~~L~~A~~
 AV~~V~~QE~~K~~E~~L~~Y~~L~~LL~~D~~PL~~A~~AV~~A~~D~~V~~AN~~H~~L~~H~~R~~C~~I~~L~~G~~M~~S~~Y~~TT~~T~~RL~~C~~TH~~R~~TE~~Y~~LER~~A~~D~~V~~LL~~M~~E~~A~~GR~~L~~I~~R~~AG~~P~~
 P~~S~~E~~I~~L~~P~~V~~Q~~AV~~P~~K~~A~~ENG~~Q~~ES~~D~~S~~A~~TA~~Q~~SV~~Q~~N~~P~~E~~K~~T~~E~~CE~~L~~EE~~E~~Q~~S~~T~~G~~R~~L~~Q~~E~~E~~S~~K~~K~~EG~~A~~VAL~~H~~V~~Y~~Q~~A~~Y~~Q~~
 W~~K~~AV~~G~~Q~~G~~LA~~L~~AI~~L~~FS~~L~~LL~~M~~Q~~A~~TR~~N~~AD~~W~~WL~~S~~W~~I~~SQL~~K~~A~~E~~NS~~S~~Q~~E~~A~~P~~ST~~S~~PA~~M~~GL~~F~~S~~P~~Q~~L~~LL~~F~~S~~P~~GN
 LY~~I~~PV~~F~~PL~~P~~X~~A~~PN~~G~~SS~~D~~IR~~F~~Y~~T~~V~~Y~~AT~~I~~AG~~V~~N~~S~~L~~C~~TL~~L~~RA~~V~~FA~~G~~TL~~Q~~AA~~T~~L~~H~~RR~~L~~L~~H~~RV~~I~~MAP~~V~~

Figure 3 - 10

FPNATPTGRILNRFSSDVACADDSPFLINILLANAAGLLGLLAVLGSGLPWLLLLPPLSIMYYHVQR
 HYRASSRELRLGSLTLSPLYSHLADTLAQLSVLRATGATYRFELENRLLELNQRCFATSATMQWLD
 IRLQLMGAAVVSAIAGIALVQHQQGLANPGLVGLSLSAISLTGLLSGLVSSFTQTEAMLVVERLEEY
 TCDLPQEPPQGPLQLGTTGWLQGGVEFDVVLAYRPGLPNALDGTFCVQPGKEKLGVGRGSGKSSL
 LVLFRLLEPSSGRVLLDGVTOTSQELAQLRSQLAIPQPFPLFSGTVRENLDPQGLHKDRALWQALKQC
 HLSEVITSMGGLDGELEGGRSLSLGQRQLLCLARALLDAKILCIDEATASVDQKTDQLLQQTICKRF
 ANKTVLTIHRLNTILNSDRVVLVQAGRVVLEDSPATLRNQPHSLFQQLQSSQQGPASLGGP

>ABCD1=ALDP= adrenoleukodystrophy protein
 MPVLSRPRPWRGNLTKRTAVLLALAAYGAHKVYPLVRQCLAPARGLQAPAGEPTQEASGVAAAKAGMNR
 VFLQRLLWLLRLFPVRVLCRETGLLHSALVSRTFLSVYVARLDGRLARCTVRKDPRFGWQLLQWL
 LIALPATFVNSAIRYLEGQLALSFRSRVLAHAYRLYFSQQTYYRVSNMDGLRNPQSLTEDVVAFAS
 VAHLYSMLTCKLDDAVTSYTLLRAARSQGTAWSAIAGLVVFATANVRAFSPKFGEVAAEARRK
 GELRYMHSRVANSEEIAFYGGHEVELALLQRSYQDLASQINLLILLERWVYMLQFLMKYVWSASGLL
 MVAVPPLITATGYSESDAEVKKALEKEEEELVSEERTAFTIARNLTTAAADAIERIMSSYKEVTEL
 YTARVHEMFQVFEDVQRCHFKRPRELEDAQAGSGTIGRSGRVREGPLKIRGQVVDVEQGIICENIPV
 PSGEVVVASLNTRVEGMHLLITGPNGCGKSSLFRILGGLWPYGGVLYKPPPQRMFYIPQRPYMSVGS
 LRDQVIYPDSVEDMQRKGYSQDLEAILDVHHLHILQREGGWEACMDWDVLDLSGGEKQRIGMARMFYH
 RPKYALLDECTSASVSDVEGKIPQAAKDAGIALLSITHRPSLWKYHTHLLQFDGEGGWKFELDSAARL
 SLTEEKQRLEQQLAGTPKMQRRLQELCQILGEAVAPAHVPAPSPQGPGLQGAST

>ABCD2=ALDR= adrenoleukodystrophy related protein
 MTHMLNAAADRVRKTRSSAAKRAACLVAAAYALKTLYPIIGKRLKQSGHGKKAAAYPAEENTEILHCT
 ETICEKPSPGVNADFFQKQLFPLPKVTTETGWLCLHSVALISRTFLSIYVAGLDGKIVKSIVEK
 KPRTFIILKIKLWLMIAIPATFVNSAIRYLECKLALAFTRTRLDHAYETTYFTNQTYKVINMDGLRANPD
 QSLTEDIMMFSQSVAHLYSNLTKPILDVMLTSYTLIQTATSRGASPIGPTLLAGLWVYATAKVLKACSP
 KFGKLVAAEAAHRKGVLRYVHSRITIANVEIAFYRGHKEMKOLQSKYKALADQMNLLSKRLWYIMIEQ
 FLMKYVWSSGLIMVAIPITATCPADGEDGQKQVMVSERTAFTARNLLASGADAIERIMSSYKEVT
 ELAGYTAARVYNNMFVWDEVKRGIYKRTAVIQESESHSKNGAKVELPSDTLAIKGKVIDVDHGIIICENV
 PIITPAGEVVVASLNPKVEEGMHLLITGPNGCGKSSLFRILSGLWPVYEGVLYKPPPQHMPYIPQRPM
 SLGSLRDQVYYPDSVDDMDKGYTDQDLERILHNHVLHYHIVQREGGWDADMWDVLDLSGGEKQRMGMR
 MFYHKPKYALLDECTSASVSDVEGKIPQAAKGACISLSSITHRPSLWKYHTHLLQFDGEGGWRFEQLDT
 AIRRTLSEEKQKLESQLAGTPKMQRNLNECLKILGEDSVLKTKIKNEDETS

>ABCD3=PXMP1= Peroxisomal membrane protein 1
 MAAFSKYLTARNSSLAGAFLLLCLLHKRRRALGLHGGKSGKPLQNNKEGKERAVIDKVFSSRLIQ
 ILKIMVPTFCETGVLVLIAVMLVSRTYCDVWMQNGTLIESGILGRSRKDFKRYLLNFIAAMPLISL
 VNNFLKYGLNELKLCFRVRLTKYLYEEYLQAFTYKMGMLDNRIANPQLLTQDVEKFCNSVVDLYSNL
 SKPFLDIVLYIFKLTSAIGAQGPASMMAYLVVSGFLTRLRRPIGKMTITEQKYEGERYVNSRLITNS
 EEIAFYNGNKRKEQTVHSVFRKLVEHLHNFILFRFSMGFIDSIIAKYLATVVGVLVSRPFLDLSPRH
 LKSTHSELLEDYYQSGRMLLRMSQALGRIVLAGREMTLLAGFTARITELMQLVKDLNHGKYERTMVSQQ
 EKCIEGVQVTPPLIPGAGEIIADNITKFDHVPLATPGNDVLIIRDNLNEVRSGANVILICGPNGCGKSSLF
 RVLGELWPLFGGRLTCKPERGKLFYVPPQRYMTLGLTRDQVIYPDGREDQKRKGISDLVLKEYLDNVQLG
 HILEREGGWDSVQDWMDVLSLGGEKQRMAMARLFYHKPQFAILDECTSASVSDVEGYIYSHCRKVGITLP
 TVSHRKSLWKHHEYYLHMDGRGNYEFQKITEDTVEFGS

>ABCD4=PXMP1L= Peroxisomal membrane protein 1-like 1
 MAVAGPAPGACARPRLDLQFLQRFLQILKVLFPSSWSSQNALMFLTLCLTLLEQFVITYQVGLIPSQYYG
 VLGNKDLEGFKTLTFLAVMLTVLNSTLKSFDQFTCNLYVSWRKDTEHLHRLYFRGRAYTLMVRDD
 IDNPQDRISQDVERFCRQLSSMASKLIIISPFTLVYYTYQCFQSTGWLGPVSIQFYFILGTVVNKTLMGP
 IVMKLVHQEKGLEGDFPRPKHMQIRVNAAFAAFYRAGHVEHMRTDRRLQRLLQTORELMSEKELWYI
 FDYLGSILSYVVIAPIFSGVYGDLSPAELSTLVSNAFVCYIILCSTQFLIDLSSTLSDVAGYTHRIG
 QLRETLDDMSLKSQDCIEGESEWGLDTPGPWPAEADTAFLERVSISAPSSDKPLIKDLSLKISEG
 QSLLITGNTGTGKTSLLRVLGGWTSTRGVSQMLTDGFPHGVFLFPQKPFDTGLREQVIYPLKEVYP
 DSGSADDERILRFLERLAGLSNLVARTEGLDQQVWDVSPGEMQRLSFARLFYLQPKYAVLDEATS
 ALTEEVESELYRIGQQLGMTFISVGHRSLEKFHSLVLCGGGRWELMRIKVE

>ABCE1= Ribonuclease L inhibitor
 MADKLTRIAIVNHDKCKPKKCQECCKSCPVRMGKLCIEVTPQSKIWISETLCIGCGICIKKCPFGA
 LSTVNLPSNLEKETTHRYCANAFKLHRLPIPRPGEVILVGTNGIICKSAALKILAGKQKPNLGYDDPP
 DWQEELTYFRGSELQNYFTKILEDDLKAIKPQYVARFLRLAKGTGVSILDRKDETKTQAIWCQQLDLT
 HLKERNVEDLSGCGELQRFACAVVCIQKADIPMFDEPSSYLDVKQRLKAATITRSLINPDRYIIVVEHDL
 SVLDYLSDFICCLYGVPSAYCVTMAPFSVREGINIFLDGYVPTENLRFRDASLTVKVAETANEVEVKKM
 CMYKPGMKKMGFELAIVAGEFTDSEIMVMLGENGTGKTTFIRMLAGRLKPDEGGEVPVNLNSVYKQ
 KISPKSTGSVRQLLHEKIRDAYTHPQFVTDVMKPLQIENIIDQEVQTLGGELQVRRLCLGKPADVY

Figure 3 - 11

LIDDEPSAYLDSEQRILMAARVVKRFLHAKKTAFFVEHDFIMATYLADRVIVFDGVPSKNTVANSPTLL
AGMNKFSLSQLITEITFRRDPNYYRPRINKLNSIKDVEQKKSGNYFFLDD

>ABCF1

MPKAPKQQPPEPEWIGDGESTSPSDKVVKGGKKDKKIKKTFEEELAIVEDKQAGEEEKVLKEKEQQQQQQ
QQQQKKKKRDRKGRRKKDVDGGEEKELMERLKLGSVPTSDEEDEVAPKPRGGKTKGGNVFAALIQQ
QSEEEEEEEKHPKPAPKPEKNRINKAVSEEQQPALKGKKGKEEKSKGKAKPQNKAALDNEEDKEEEI
IKEKEPPKQGKEKAKKAQEOMEYERQVASLKAANAAENDFSVSQAEMSSRQAMLENASDIKLEKFSISAH
GKELFVNADLYIVAGRYGLGVPGNGKGTLLKHIANRALSTPPNIDVLLCEQEVADETPAVQAVLRA
DTKRLKLLEERRLQGQLEQGDDTAAERLEKVEELRATGAAAEEAKARRILAGLGDFPEMQRPTQKF
SGGWRMRVSLARALFMEPTLLMLDEPTNHLDLNIAVILNNYLGWRKTLLIVSHDQGFLDDVCTDIIHL
DAQLHYYRGNYMTFKMYQQKQKELLKQYEKQEKKLKELKAGGKSTKQAEKQTKEALTRKQKCRRN
QDEESQEAPELLKRPKEYTVRFTFPDPPLSPPVLGLHGVTFGYQGQKPLFKNLDFGIDMDSRICIVGP
NGVGKSTLLLTLTGKLTPTGEMRKNHRLKIGFPNQOYAEQLRMEETPTEYLQRGFNLPYQDARKCLGR
FGLESHHTIYICKLSGGQKARVMVFAELACREPDLILDEPTNNLDIESIDALGEAINNEYKAVIVSH
DARLITETNCQLWVVEEQSVSQIDGFDYKREVLREALGEVMVSRPRE

>ABCF2

MPSDLAKKKAACKKEAAKARQRPRKGHEENGDVVTEPQVAEKNANGRETTEVDLLTKELEDDEMKA
ARAVTGVULASHPNSTDVHIIINLSLTFHGQELLSDTKLELNSGRYGLIGLNGIKSMLLSAIGKREVPI
PEHIDIYHLTREMPPSDKTPLHCVMEDTERAMLEKEAERLAHEDAEC EKLMELYERLEELDADKAEMR
ASRILHGLGFTPAMQRKKLDFSGGWRMRVALARALFIRPFMLLDEPTNHLDLACVWLEEEELKTFKR
ILVLVSHSODPLNGVCTNLLHMHNKKLYYTGNYDQVTRLEENQMKRFHWEQDQIAHMKNYIARF
GHGSAKLRQAQSKEKTLQKMMASGLTERVSDKTLSPFPPCGKIPPPVIMVNQVSKYTKDPCIYN
NLEFGIDLDTRVALVGPNGAGKSTLLKLLTGEELLPTDMTRKHSVHIGRYHQHQBOLDLDSPLEYM
MKCYPEIKEEEMRKIITGYGLTGKQQVSPIRNLSDGQKCRVCLAWLAWQNPQHMLFLDEPTNHLDIETI
DALADAINEFEGGMLVSHDPRLIQQVAQEIWVCEKQTITKWPGDILAYKEHLKSKLVDEEPQLTKRTH
NVCTLTLASLPRP

>ABCF3

MATCABILRSEFPEIDGQVFYVTGVLHSGSADFESVDDLVEAVGELLQEVSQDSKDAGIRAVCORMY
NTLRLAEPOSQGSQVLLDAPQLSKITENYDCGTLPCLLKREQSSTVNAKKLEAKEARLKAKQEKRS
EKDTLKTTSNPVLEEAASQAGSRKESRLESSQGKNSYDVRNFIENFDVSFGDRVLLAGADVNLAWGRRYG
LVGRNGLGKTTLLKMLATRSRVPATHSLLHVQEVAQDDTPALQSVLESDSVREDDLRRRELAETQIA
AGRAEGSEAAELAETIYAKLEEIEADKAPARASVILAQLGFTPKMQQQPTREFSGGWRMRLALARALFAR
PDLLLLDEPTNMLDVRAILWLNEYLQTPSTILVVSNDRNFLNAIATDIIHLHSQRLGYRGDFETFIK
SKQERLLNQREYEAQQYRQHIIQVFIIDRFRYANRASQVSKLMLKLEPELRPVDEKESEVVMKFPDG
FEKFSPPIQILDEVFYYDPKHFVFSRLVSADLESRICVUGENGAGKSTMKLLLGD LAPVRGIRAH
RNLKIGYFSQHHVQLDNLNVSAVELLARKFPGREEEYRHOLGRYGISGELAMRPLASLSGGQKSRVAF
AQMTMPCPNFYIILDEPTNHLDMETIEALGRALNNFRGGVILVSHDERFIRLVCRELWVCEGGGVTRVEG
GFDQYRALLQEQRREGFL

>ABCG1=ABC8 WHITE protein homolog

MAAFSGVTAMNASSYSAEMTEPKSVCSVDEVVSSNMEATETDLLNGHLKKVDDNNLTEAQRFS SLPRRA
AVNIEFRDLSYSVPEGPWRRKGYKTLKGISGKFNSELVAIMPAGKSTLMNLTLAGYRETGMKG
VLIINGLPRDLCRKRKVSCYIMQDDMLPHLTQFQAMMSAHLKLOEKDECRRREMVKIELTALGLLSCAN
TRTGSLSGGQRKRLATALELVNNPPMFFDEPTSGLDASASCQVSVSLMKGLAQGGRSIICITHQPSAKL
FELFDQLYVLSQGQCVYRGKVCNLVPYLRDGLNCPTYHNPQDFVMEVASGEYGDQNSRLVRAVREGMC
DSDHKRDLGGDAEVNPFLWHRPSEEVKQTKLRLKLRKDSSSMEGCHSFASCLTQFCILFKRTFLSIMR
DSVLTHLRITSHIGIGLLIGLLYLGIGNETKKVLSNSGFLFFSMLFLMFAALMPTVLTFLMEGVFLRE
HLNLYWSLKAYYLAKTMADVPFQIMFPVAYCSIVYWMTSQPSDAVRFLFAALGTMTSIVQSLGLLIG
AASTSLQVATFVGPTAIPVULLFSGFFVSFDTIPTYLQWMSIYSYVRYGFEVILSIYGLDREDLHCDI
DETCHFQKSEALRLDENAKLYLDFIVLGIFFISLVLRYKIRAER

>ABCG2= BCRP or Breast Cancer Resistance Protein

MSSSNVEVFIPVSQGNTNGFPATVSNLKAFTGAVLSPFHNICYRVLKSGPLPCRKPVEKEILSNING
IMKPGLNAILGPTGGGKSSLVDLAAKDPGSLSGDVLINGAPR PANFKCNNSGYVVQDDVVMGTLTVRE
NLQFSAALRLATTMTNHEKNERINRVIIEELGLDKVADSKVGTQFIRGVSGGERRTSIGMELITDPSIL
SLDEPTTGLDSSTANAVLLLKRMKSQGRTIIFSIHQPRYSIFKLFDSLTLASGRLMFHGPQAEGALY
FESAGYHCEAYNNPADFLDIINGDSTAVALNREEDFKATEIIEPSKQDKPLIEKLAEIYVNSSFYKET
KAELHQLSCGEKKKKITVFKIESYFTSFCQHRLWVSKRSFKNLLGPNQASIAQIIVTVVVLGLVIGAIYF
GLKNDSTGIQNRAGVLFFLTTNQCFSVSAVELFVVEKKLFIEHEYISGYYRVSSYFLGKLLSDLLPMMR
LPSIIEFTCIVYFMLGLKPKADAFFVMFTLMMVAYASSMALAIAQSVSVSVALLMLTICVFMMIFS
GLLVNLTTIASWLSLWQYFSIPTYGFTALQHNEFLGQNCFCPGLNATGNPCNYATCTGEEYLVQGIDL
SPWGLWKNNHALACMIVFLTIAYLKLLFLKKYS

Figure 3 - 12

>ABCg5

MGDLSSLTGGSMGLQVNRGSQSSLEGAATAPAEPHSLGILHASYSVSHRVRPWDITSCRQQWTRQIL
 KDVSLVYVESCGOIMCILCGSSGSKTTLLDAMSGRLGRAGTFLGEVVNGRALRREQFQDCFVSVLQSDTL
 LSSLTVRETLHYTALLAIRGNPGSFQKKVEAVMAELSLSHVADRLIGNYSLGGISTGERRRSIAAQL
 LQDPKVMLPPTGDCMTANQIVVLLVBLARRNRIVVLTIHQPRSELFDKIAILSPGELIFCGTPA
 EMMLDFNDCCGYPCEHNSFDFYMDLTSVDTQSKEREIETSKRVQMIESAYKSAICHKTLKNIERMKH
 LKTLPLMPFKDKSPGVPSKLGVLRRVTRNRLVRNKLAIVTRLLQNLIMGLPLLFFVLRVRSNVLKGA
 QDRVGLLYQVGATPYTGMLNAVNLFVLRRAVSDQESQDGLYQKQWQMLAYALHVLPPFSVVATMIPSSV
 CYWTGLLHPEVARFGYFSALLAPHLIGEFLTLVLLGIVQNPNIVNSVVALLSLAGVLVGSGFLRNQIE
 MPIPFPKILSYTFQKCYSEILVNVNEFYGLNFTCGSSNVSVITNPMCAPTQGIQFIEKTCPGATSRFTMN
 FLILYSFIPALVILGIVVFKIRDHLISR

>ABCg8

MAGKAAEERGLPKGATPPQDTSGLQDRLFSSEDNSLSLYFTYSGQPNTLEVRDLNYQVDLASQVFWFQELA
 QPKMPWTSPSCQNSCELGTQNLSPKVRCQMLAIIGSSCCGRASLLDVITGRHGKGKIKSGQJWINGQP
 SSPQLVRKCVAHVRQHNQLLPNLTVRETLAFIAQMRLPRTFSQARDKRVDEVIAELRLRQCADTRVGN
 MYVRGLSGGERRRVSIGVQLLNPGILILDEPTSGLDSFTAHLVNLVKTLSRLAKGNRLVLSLHQPRSIDI
 ERLFDLVLLMTSGTPYIYLGAQHMVQYTAIGYPCPRYSNPADFYVVDLTSIDRRSREQELATREKAQSL
 AALFLKEVRLDDFLWKAETKDLDEDTCVESSVTPLDTNCLPSPTKMPGAVQOPTTLIRRQISNDFRDL
 PTLLIHGAECALMSMTIGLYFGHGSQIQLSFMDTAAFLPMIGALIPEFNVIDVISCKYSERAMLYYELE
 DGLYTTGPYFFAKILGELEPHCAYIIITYGMPYTWLANLRPGLQPFLLHFLLVWLVVFCCRIMALAAAAL
 LPTFHMASFFSNALYNSFYLAGGFMINLSSLWTVPAWISKVSPRLWCFEGLMKIQFSRRTYKMPGLNLT
 TAVSGDKILSVMELDSYPLYAIYLIVIGLSSGFMVLYVSLRFIKQKPSQDW

Bacterial Transporters (examples)

>LmrA= lincomycin resistance protein

MERGPQMANRIEGKAVDKTSIKHVFVKLIRAAKPRYLFVFIGIVAGIITGLTQLOVPKMVQPLINSFGHG
 VNGGKVALVIALYSAVSAIAIVLGCESVVKNLRLTRVWDMHILPVKYFDEVKTGEMSRLAND
 TTQVKNLIANSIPOAFTSILLVGSIIFMLQMQWRLTLAMIIVLPVIMLIIMFPIMTFCQKIGWTRQDSL
 ANFQGIASESLSSEIRLVKSNSAEKQASKKAENDVNALYKIGVKEAVFDGLMSPVMLSMSMLIFGLLAY
 GIYLISTGVMSLGLTLLGMMMYLMNLIGVUPPTVATFTELAKASGSTGRLLTELLDEEQEVLHQGDSDL
 GKTLSAHHVDFAYDDSEQILHDSEFAQNSIIIAFAGPSGGKSTIFSLLERFYQPTAGEITIGGQID
 SVSLENWRQSQIGFVSDQSAIMAGTIRENLTYGLEGNFTDEDLWQVLDLAFARSFVENMPDQLNTEVGER
 GVKSISGGQRQLAIARAFLRNPKILMLDEATASLDSESESVMQRAIDLQSLMKGRTTLVIAHRLSTIVDAD
 KIYFIEKGEITGSGKHNELVATHPLYAKYVSEQLTVQG

>DrrA=daunorubicin resistance protein

MNTQPTRAIETSGLVKVYNGTRAVDGLDLNVPAGLVYGLGPGNGACKSTTIRMLATLLRPDGGTARVFG
 HDVTSEPDVRRRISVTGQYASVDEGLTGTENLVMGRLQGYSWARARERAELIDGFLGDDARDLLK
 TYSGGMRRRLDIAASIVTPDLLFLDEPTGLDPRSRNQVWDIVRALVDAGTTVLLMTQYLDEADQLAD
 RIAVIDHGRVIAEGTTGELKSSLGSNVRLRLHDAQSRAEAERLLSaelGVTHRDSDPTALSARIDDP
 RQGMRALAELSRTTHEVRSLFSLGQSSLDEVFLALTGHPADRSTEEAAEEEKVA

>OleB=oleandomycin resistance protein Streptomyces coelicor

MQNAHRSDTGAAALTGTPEKLLPTQPETGSFQVVLDDVVRAPGGPRLLDGVNVQSVALGERVGIIGENG
 GKSTLLRMLAGVDRPDGGQVLVRAPGGCGYLQPTPDLPPEPDVQDADHALAELRSLERGLREAEQALA
 GAEPPEELEGILLGAYGDLLEERFAYAadarvdaAMHGLLAGITGDRLGSLSGGEQARLNLACLLLA
 ASPQLMLDEPTNHLDVGALEWLEERLRAHGSVLUVSHDRVFLERVATLWEVDGERRTVNRHGGYA
 GYLQAKAAAARRRWEQAYQDWLEDALARQRELARSAADHLATGPRRNTERSNQRHQRNVEKQISARVRNA
 ERVRRLEENPVPRPPQPMRFRARVEGGGTVGRGGALAELEYKVTVGTRLDVPSFTVDPGERILITGHNGA
 GKSTLLRVLGDLAPDQGECERPERIGLWPQETEITDRQSSLAAFAAGLPGIAEEHRGALLGFGFLFRP
 SALCTAVGDLSTGQLRRLLARLLRDPADLLLDEPTNHLSPALVEDLEEALAHYRGALVVVSHDRMFA
 QRFTGRRMHMEGGRFVE

PROTOZOA (examples)>Pfmdr2= multidrug resistance protein 2 - malaria parasite
(Plasmodium falciparum)

MDVSNYEYLSYGIKNEKLKRKRTHKKIIIIYHLLDIIIFFLFFSCYNPNLELCYKYEKAIFYNFFKSSV
 DLFLLNVIRIIYTIVLFRHKKLTELNTLGKVVLRSRHTGILVILVNIKMINYSYVIKSENPLYNTNM
 YLITLKVLFMVYMSIISIYYYFIQFKLYNKKYIARVELEKILINDIKSKKYNIIYKSDENSGLLGTD
 NNSTIMNNEYLNLDYKLNLLDMNISYNKLNKINNDIINNTSDVQEKNMDYNDIHFQKKKKSSNPAYLN
 FFHKESKDNCIDVKEFLNKRYGSNKRSSKIYDNNNNNNNNNNINSKIDYLENNITYTEFKKILLPYLW

Figure 3 - 13

PSKRIDMKGNSSILRTYIVLIFLPILVSKFVSVISPIYLGWASNEVLKKSLSVVYLYVTFFFISK
 FLKEVCVGVLPSVQQSAFIELQESIFQTFHNLSEWYSSKGIMRIVDRGTESANNLMSSVLMYIIP
 ATIEGLITCIIIFIFKYKNSLILGSVLFIGLTLYIYSTIKITKWRKKIRTKANEMDNVYHDIAHDSLTYE
 NVKYFSNEKFBIKKFCNCALSNYHRYNLKILNSLGILNVTQQFILNGTLFFTLLCVIYMTIVKEGSDPGTF
 ISVVVYTSNVFAPLSILGTLVYIQSFTDISDLIDILRKDIDISNDKLNKFDLTSQEKKPGVSIEFN
 NVHFMYPPTOPLHTSLKDINIVYIKPGTTCALVGHGTGSKTISKLLYRFYDSKGEIKIGGRNINEYTRNS
 IRNIIGIVPQDTILFNESIKYNILYGKLDATEEEELIQAVKSAQLYDFIQSLPKKWDTLVGDKGVKLSGG
 ERQRISTARCLLKDPKIVIFDEATSSLDSRTEYLQKAVEDLRKNRTIIIAHKLCTTTAELILLNK
 GKIIERGTHLDLLKCNGEYTEMWNMQSKSNEPHETETNSSIDKDDVNKNNNKNNNDVILNTCKNDITTSFR
 SNSEKSSQEFSDASNHIKQSKTSNDHNNNINVHKKNEQELPLTNKDMDDNMNNKKK

>DVLQF=MDR-PLAFF= Pfmr1= chloroquine resistance protein (*Plasmodium falciparum*)
 MGKEQREKKDGNLISIKEEVEKELNKSTAEFLRKIKNEKISFFLPPFKLPAQHRKLLFISFVCAVLSSG
 TLPFFISVFGVILKNMNLGDDINPIILSLSVSIGLVQFILSMISSYCDMVITSKILKTLKLEYLRSVFYQ
 DGQFHDDNPGSKLRSDDLFYLOVSSGIGTKFPTIFTYASSFLGLYIWSLIKNRALTLCITCVFPLIYV
 CGVICNKKVKLNKKTSLLYNNNTMSIIEALMGIRTVASYCGEKTILNKFNLTSETFYSKYILKANFVEA
 LHIGLINGLILVSYAFGFYWYGTTRIISATNQYPNNDNGASVISILGVLISMFLTIILPNITEYMK
 ALEATNSLYYEIINRKPLVENVNDGETLPNKKIEFKNVRFHYDTRKDVIEYKDLSTFLKEGKTYAFVGE
 SGCGKSTILKLLERLYDPTEGDIIVNDSHNLKDINLKWWRSKIGVVSQDPPLLFSNSIKNNIKYSLYSLK
 DLEAMENYYEENTNDTYENKFLSILSNMTSNELEMKEYQTIKDSDDVDSKKVLIHDFVSSLPDKY
 DTLVGSNASKLSSGGQKQRIARAIMRNPKILILDEATSSLDNKSEYLVQKTIINNLKGNEENRITIIIAH
 RLSTIRYANTIFVLSNRERSDNNN
 INNQKISSNKSNNNGNDNGSDNKSAYKSDTGNDADNMNSLISIHENENISNNRNCKNTAENEKEEKVP
 FFKRMFRKKKAPPNLRLIYKEIFSYKDVDTIIIFPSILVAGGLYPVFAFLYARYVSTLEFDANLEYNSN
 KSYIYILLIAIAMFISETLKNNNNKIGEKVEKTMKRLPENIYLQEMSFFDQDKNTPGVLSAHINRDV
 HLLKTGGLVNNIVIFSHFIMLFLVSMVMSFYFCPIAAVLTFTIYFIMMRVFAVRARLTKSKEIEKENMS
 SGVFAFSSDEMFKDPSFLIQEAFYNNMHTVINGLEDYFCNLIEKAIDYKNKGQKRRIVNAALWGFQS
 SAQLFINSVAFWFGSFLIKRGTLVTDKVNFRYISRPNPVIYKNLSTCDSKKTTAIVGETGSGKSTFMNL
 SNIDVRDDGGRINKNLIKKGKVDIKDVNFYIISRPNPVIYKNLSTCDSKKTTAIVGETGSGKSTFMNL
 LLRFYDLKNDHILKNDMTNFQDYQNNNNNSLVLKVNNEPSNQSGSAEDYTVDNNNGEILLDDINICDY
 NLRLDLRNLFSTIVSQEPMFNMMSIYENIKFGREDATLEDVKRVSKAIADEPIESLPNKYDINVGPyGKS
 LSGGQKQRIAIARALLREPCKILLDEATSSLDSNSEKLIETIIVDIKDAKTIITIAHRIASIKRSOK
 IVFNNPDRNGTFVQSHGTHDELLSAQDGIYKKYVKLAK

>DVLNS= Methothrexate resistance protein *Leishmania tarentolae*
 MVDNGHVTIAMADLGTVVETAQVRCQEAQRKFAEQIDELWGGEPTVTPEDQASWFQOLYYGWIGDY
 TYKAAAGNITEADLPPPTRSTRTYHIGRKLSRQAHADIDASRQHADLQVWQYIGCEVYVKEAEAKGVLRWVGH
 LQQSDYPRSLVAGVEWRMPPRHLRAVLGSAALHNGVHGERLFPHEDNYLCSCCEPVEQLVVKSKYN
 LIPIPPRPPPSPDLLRTLFLKVHWYHVWAQILPKLSSDVTALMLPVLLFYVKYLNADNATWGWLGLALTI
 FLTNVIQSCSAHYDHISIRTAALFETSSMALLFEKCFTVSRRSLQRPDMSVGRIMNMVGNDVNIGSL
 NWYVMYFWSAPlQLVLCLLLIRLGVWLRVGMALFVTLPLQAVISKHQVQDVSERMASVVDLRIKRTN
 ELLSGVRIVKFMGWEPVFLARIQDARSRELRCRDLRVHVNFFMVNDATPTLVIAVVFILYHVGKVL
 KPEVVFPTIALNTMRSVFFMIPIIISSLQCFVSAKRTAFIECPDTHQSQVQDITASIDVPAAAIFKG
 ASIHTYLPVKLPRCKSRLTAMQRSTLWFRRRGVPETEWEYEDSPDASSLAVHSTTVHMGSTQTVITD
 SDGAAGEDEKGEVEEGDREYYQLVSKELLNRVSLTIPKGKLTMVIGSTGSKSTLLGALMGEYSVESGE
 IWAERSIAYVQQAWIMNATLRGNILFDEERAEDLQDVIRCCQLEADLAQFCGGLDEIGEMGVNLSG
 GQKARVSLARVYANRDVYIIDDPLSALDAHVGQRIVQDVILGRLKTRVLATHQIHLLPLADYIVVL
 QHGSIVFAGDFAFSATALEETLRGELKGSKDVECSSDVTESATAETAPYVAKAGLNAEQETSLAG
 GEDPLRSDVEAGRLMTTEKATGKPVWSTYVAYLKCSCGLEAWGCLLATFALTECVAASSVWSIYST
 GSLSMWSADTYLVVLFIVFLFEGSPFLFCYLYIRIGSRNMHRDLESIGVARMSFFDTTPVGRVLN
 RFTKDMISLDNTLNDGYLYLLEQFFSMCSTVILMVVQPFVLLVAVPCVYSSYKLMQVYNAASNRETRRI
 KSIAHSPVFTLLEESLQGRTIATYGKLHLVQEARLGRDLYVSYALVMQNVSNRWLGVRLFSCVUTF
 MVAFIGVIGKMEGASSQNIGLISLSTMSTLTETLNWLVRQVAMEANMNSVERVLHYTQEVEHEHP
 EMGELVAQLVRSESGRGANVTETVVIESAGAASSALHPVQAGSLVLEGVQMRYREGLPLVLRGVSPQIA
 PREKVGIVGRTGSKSTLLTFMRRMVEVCGVIHVNREMSEAYGLRELRHFMSIPQDPVLFDGTVRON
 VDPFLEASSAEWAELVGLRERVASESEGIDSRLVEGGSNYSVGQRQLMCMARALLKRGSGFILMDE
 ATANIDPALDRQIATVMSAFSAYTVITIAHRLHTVAQYDKIIVMDHGVVAAEMSPRELVMNHQSMPHS
 MVEGLSGRSKDFYELLMGRRIVQPAVLS

FUNGAL TRANSPORTERS (examples)

>Bfr1= Brefeldin A resistance protein *Schizosaccharomyces pombe*
 MNQNSDTTHGQALGSTLNHTTEVTRISNSSDHFEDSSNVDESLDSSNPSSNEKASHTNEEYRSKGQNS
 YVPSSSNEPSPESSSNSDSSSDSSVDRLAGDPFELGENFNLKHYLRAYKDSLQRDDIITRSSGVCMR
 DHSVYGVGSGYEFLKTFDIFLQPYRAITEKQVVEKAILSHCHALANAGELVMVLGQPGSGCSTFLRSV

Figure 3 - 14

TSDTVHYKRVEGTTHYDGIDKADMKKFFPGDLLYSGENDVHFPSLTTAETLDFAAKCRTPNRPNCLTR
 QEVYRSERHLLIATAFGLTHTFTKVGNDFVRGVSGGERKRVTISEGCFATRPTIACWDNSTRGLDSSSTAF
 EFVNVLRTCANELKMTSFVTAYQASEK1YKLFDRCIVLYAGRQIYYGPADKAKQYFLDMGFDCHPRETT
 PDPFLTAISDPKARFPRKGFPENRVPRTPDFEPMQRNSVYADLMAEMESYDKRWTEPPASSEAPEKD
 FGSDISATTKHELYRQSVAEKSFRVKDTSPTYTFSQQLWYCLARSWERYINDPAYIGSMAFAFLQS
 LIIGSIFYDMKLNTDVFSRGGVLFSSILPCALQSLSEIANMFSQRPIIAKHRASALYHPAADVSSL
 VDLPFRFINISVFSIVLYFLTNLKRTAGGWFTYFLFLFIGATCMSAFRSLAGIMPNVESASALGGIGV
 LAIAIYTYGAIPNIDGVWGRFWIAYLPLQFGEFSLMINEFKARQFECQSLIPYGSYDNPVANKICP
 VTSAEPGTVDGSTLY1SFNYKTRQLWRNLAI1IIGYAFLVFVNIVASETLNFNDLKGEYLVFRGH
 APDAVKAANNEGGKPLDLETGQDTQGGDVKWESPDNEEELNKEYEGIEKGHDIFSWRNLYNDIQIKEH
 RRLLNQVQGFVVPGKLTALMGESGAGKTLLNVLQAQRVDTGVVTGDMLVNGRGLDSTFQRRTGYVQQQD
 VHIGESTVREALRFSAAALRQPASVPLSEKYEVVESVIKLEMESYAAIIGTPGSLNVEQRKRATIGV
 ELAAKPALLFLDEPTSGLDSQSAWSIVCPLRKLADAGQAILCTIHQPSAVLFQDRLLLQKGKTV
 YFGDGEHSKTLNNYFESHGKDFDDGNPAAI1LDVIGAGATATTNDRWHEVWNNEERKAISAELDK
 INASPSNSEDKKTLSKEDRSTYAMPLWFQVKMVMTRNQFQSYWREPSILMSKLALDIFAGLFIGFTFYNQ
 GLGVQNIQNKLFAVFMATVLAVPLINGLQPKFIELRNVFEVREKPSIYSWVAFVFSAIIVEIPFNLVF
 GTLFFLCWFYPIKFYKHHHPGDKTGYAWLLYMFQMYFSTFGQAVASACPNAQTASVUNSLFTFVIT
 FNGVLQPNNSLNGFWHWMHSLTPFTYIEGLLSDLVHGLPVECKSHMLTINPPSGQTCGEYMSAFLT
 NTAAGNLLNPNATTSCSYCPYQTAQFLERPSMRYTHRWRNLGI1FVGYVFFNIFAVLLLFTYVFRVMKLR
 STWLGKKITGTG

>Cdr1= multidrug resistance protein 1 *Candida albicans*

MDSKMQSSQESKLEKAISQDSSSENHSINEYHGFDATHNTFTHDSFKDDSSAGLLKYLTH
 MSEVPGVNPYEEHEEINNDQLNPDSENFNAKFWVKNLKLFESDPEYYKPSKLGIGYRNLRAYGVANDSD
 YQPTVTNALWKLATEGFRHFQKDDDSRYFDILKSMDAIMRPGELTVVLRGPAGCSTLLKTIAVNTYGP
 HIGKESQITYDGLSPHDIERHYRGDVIYSAETDVHFPHLSVGDTLEFAARLRTPQNRGEIDRETYAKH
 MASVYMATYGLSHTRNTNVGNDFVRGVSGGERKRVSIAEASLSGANIQCWDNAATRGLDSATALEFIRAL
 KTSAVILDTPPLAIYQCSQDAYDLFDKVVVLYEGYQIFFGKATAKEEYFECRERSNTRETYRESHVAKQSNT
 RPASPYTVSFQMVRGVARNPLRMKGDPSPISIFSVFGQLVMGLILSSVFYNSQTTGSFYRGAAMFF
 AVLFPNAFSSLLEIMSLEFEARPIVEKHKKYALYRPSADALASI1SELPVKLAMSMSFNFVVFYFMVNFRRN
 PGRRFFYWLMIWCTFVMSLHVRGKVSATSI5GAMTPAIVLLAMVYTGFV1PTPSMLGWSRWINYI
 NPVGYVFESLVMNEFHCREFCQCAQYVPSGPYEN1SRSNQVCTAVGSVPGNEMVSGTNYLAGAYQYYNS
 HKWRNLGITIGFAVFFLAITYIALTEFNKGAMQKGEIVLFLKGSLKKHRRKTAASNKGDIEAGPVAGKLD
 YQDEAEAVNNEKTFEKGSTGSVDFPENRBIFFWRDLTYQVKIKKEDRVLIDHVDGVVKPGQITALMGAS
 GAGKTTLLNCLSERVTGTTIITDGERLVRNGHALDSFQRSIGVQOQQDVLHPTSTVREALQFSAYLRQSN
 KISKKEKDDYVODVYDILLEMTDYADALVGAGELNVEQRKRLTIGVELVAKPKLLLFLDEPTSGLDSQ
 TAWSICKLMLRKLAHDHGQAILCTIHQPSALIMAEDRLLFLQKGRTAYFGELEGNCQTMINYFEKYGAD
 PCPKEANPAEWMQLVVGAAAPGSHAKQDYFEVWRNSSEYQAVREEINRMEAELSCLRNDPDEALLKYAA
 PLWKQYLLVSWRTIVQDWRSRPGYIYSKIFLVSAAFLNGFSFKAKNNMQLQNQMFSVFMFIIPNTL
 VQQMLPYFVKHRADVYEVREAPSRTFSWFAFIAGQITFVQAVGTLIAFFCWYYPGLYNNATPTDSV
 NPGVLMWMLVTAFYVYTATMGQLCMSFSELADNAANLTLFTMCILFCGVLAGPDLPGFWIFMYRC
 NFPTYLVQMLSTGLANITFKCAEREYVSVKPPNGESCSTYLDPYIKFAGGYFETRNDGSCAFCQMSST
 NTFLKSVNSLYSERWRNFGIFIAFIAINIILTV1FYWLARVPKGNREKKNNK

>Cdr2= multidrug resistance protein 2 *Candida albicans*

MSTANTSLSQLDENPWPWDASDNSSVQEYQGFDATA SHN1QDLARKLTHGSTNGDHHSANDLARYLSHM
 SDIPGVSPFNGNISHEQLDPSENFNAKYWVKNLKLFESDSDYYKPSKLGIVRNLRAYGTAINDSDYQ
 PTVTNALWKPTTEAINKLKKPDDSKYFDILKSMDAIMRPGELTVVLRGPAGCSTLLKTIAVNTYGFHI
 GKEQSQITYDGLSPHDIERHYRGDVIYSAETDVHFPHLSVGDTLEFAARLRTPONRGEIDRETYAKHMA
 SVYMATYGLSHTRNTNVGNDFVRGVSGGERKRVSIAEASLSGANIQCWDNAATRGLDSATALEFIRALKT
 SATILDTPPLAIYQCSQDAYELPDNVVVLYEYGQIFFGKASKAKEYFENMGWKCPCQRQTTADFLSLT
 NPAEREPLPGYEDKVPRTAQEFTFWNSPEYAEELTKIDEYFECRERSNTGETYRESHVKGQSNTRP
 SSPYTVSFQMVRGVYIARNFLRMKGDPSPILISILSQLVMGLILASVFFFNLKSTDFTYFRGGALFFSV
 LFNAFSSLLIEILSLLYEARPIVEKHKKYALYRPSADALASI1SELPVKLMTMSFNIVYYFMVNLLRTAG
 NFFFFYWLMLCASCTLVMSHMFRS1GAVTTIATAMSLSTVFLLAMI1IYAGFVLPIPYILGWSRWRVYINP
 VTY1FESLMVNEFHGREFFCGQYIPSGCFENLPVENKVCFTVGSTPGSTVVQGTEY1KLAYQFVSSHK
 WRNFGITVAFVFFLGVYVALTEFNKGASQKGEIVLFLKGSLKKHRRKTAASNKGDIEAGPVAGKLDYQ
 DEAEAVNNEKTFEKGSTGSVDFPENRBIFFWRDLTYQVKIKKEDRVLIDHVDGVVKPGQITALMGASGA
 GKTTLLNCLSERVTGTTIITDGERLVRNGHALDSSFQRSIGYVQOQQDVLHETTTVREALQFSAYLRQSNKI
 SKKEKDDYVODVYDILLEMTDYADALVGAGELNVEQRKRLTIGVELVAKPKLLLFLDEPTSGLDSQTA
 WSICKLMLRKLAHDHGQAILCTIHQPSALIMAEDRLLFLQKGRTAYFGELEGNCQTMINYFEKYGADPC
 PKEANPAEWMQLVVGAAAPGSHAKQDYFEVWRNSSEYQAVREEINRMEAELSCLRNDPDEALLKYAAPL
 WKQYLLVSWRTIVQDWRSRPGYIYSKIL1LVISSSLFIGFSFFKSKNNLQGLQSMLAVFMFFVPFTTID
 QMLPYFVKHRADVYEVREAPSRTFSWFAFIAGQITSE1PFQIVVGTISYFCWYYPGLYANAEPDSVNS
 RGVLWMLLTAFYVYTSTMGQLAISLNEI1DNAANLATLFTCLMFCGVLAGPNV1PGFWIFMYRCNP

Figure 3 - 15

FTYLIQAILSTGLANAKVTCAPRELVTLLKPPMGETCSSFIGPYTEAAGGYFSTNSDGTCSVCRIDSTNQ
FLESINALFSQRWRNFGIFVAFIGINIILTIFFYWLARVPKGNRREKKMKK

>Pdr5p= multidrug resistance transporter *Saccharomyces cerevisiae*
 MPEAKLNNNVNDVTSYSSASSSTENAADLHNNGFDEHTEARIQKLARTLTAQSMQNSTQSAPNKSDAQ
 SIFSSGVEGVNPISFDPEAPGYDPKLDPNSENFSAAWVKNMAHLSAADPDFYKPYSLGCAWKNLSSASG
 ASADVAYQSTVVNIPIYKILKSGLRFQRSKETNTFQILKPMGDCLMPGEELLVVLGRPGSGCTTLLKSIS
 SNTHGFDLGADTKISYSGYSGDDIKKHFRGEVYNAEADVHLPHLTFTETLVTVALKTPQNRIKGVD
 ESYANHLLAEVAMATYGLSHTRNTKVGNDIVRGVSGGERKRVSIAEVSEICGSKFOCWDNATRGLDSATAL
 EFIRALKTOADISNTSATVAIYQCSQDAYDLFNKVCVLDDGYQIYVGPADKAKKYFEDMGYVCPSRQTT
 ADFLTSVTPSPERTLNKDMKLGKIHIPQTPKEMWVKSPNYKELMKEVDQRLLNDEASREAIKEAH
 IAKQSKRARPSSPTVSYMMQVKYLIRRNMWRLRNNIGFTLFMILGNCMSALILGSMFFKIMKKGDTST
 FYFRGSAMFAILNFNAFSLLEIFSLYEARPITEKRTYSLYHPSADAFASVLEIPSCLIIAVCFNI
 IYFLVDFRRNGVVFYLLINIVAVFSMSHLFRCVGSLLTKTLEAMVPASMLLLALSMYTGBAPIPKKI
 LRWSKWIWYINPLAYLFESLLINEFHGIKFPACAEEVPRGPAYANIISSTESVCTVVGAVPGQDYVLGDDF
 IRGTYQYYHKDKWRCFGIGMAYVVFVYFLCEYNEGAQKGEILVFPRTSIVKRMKKRGLVTEKNA
 DPENVGERSDSLSSDRKMLQESSEESDTYGEIGLSKSEAIFHWRNLCYEVQIKAETRRILNNVNDGWVKP
 GTLTALMGASGAGKTTLLDCLAERVTMGVITGDLIVNGIPRDKSFPRSIGYCCQQQDLHLKTATVRESLR
 FSAYLROPAEVSIEEKNRVEEVKILEMEKYADAVVGVAEGEGLNEQRKRLTIGVELTAKPKLLVFLD
 EPTSGLDSQTAWSICQLMKLANKHQAILCTIHQPSA1MQEFDRLLFMQRGGKTVYFGDLGECCKTM
 DYFESHGAHKCPADANPAEWMLEVVGAAAGPSHANQDYYEWWRNSEEYRAVQSELDMERELPKKGSITA
 AEDKHEFSQSILYQTKLVSIRLFQQYWRSPDYLWSKFILTIFNQLFIGFTFKAGTSIQLQGLNQMLAVF
 MFTVIFNPIILQQYLPSPVQQRDLYEARERPSRTFSWISFIFAQIFVEVPWNILAGTIAYFIYYPGFY
 SNASAAGQLHERGALFWLFSCAFYVYVGSMGLLVISFNQVAESAANLASLLFTMSLSFCGVMTTPSAM
 RFWIFMYRVSPLTYFIQALLAVGVANVDVKCADYELLEFTPPSGMTCGQYMEPYLQLAKTGYLTDENAT
 DTCFCQISTTNNDYLANVNSFYSERWRNYGIFICYIAFNFIAGVFYWLARVPKKNGKLSKK

>Sng2P *Saccharomyces cerevisiae*
 MSNIKSTQDSSHNAVARSSSASFAASEESTGITHDKDEQSDTPADKLTKML/TGPARDTASQIISATVSE
 MAPDVVKVESFADALSRHTTRSGAFNMDSDSDDGFDAAIFESFVRDADEQGIHIRKAGVTIEDVSAK
 GVDASALEGATFGNILCLPLTIFKGIIKAKRHQKMRQIIISNVNALAAEAGEMILVLRPGAGCSSFLKVTA
 GEIDQFAGGVSGEVADGIPQEEMMKRYKADVIYNGELDVHFPLTVKQTLDFAIACKTPALRVNNVSK
 KEYIASRRDLYATIFGLRHTYNTKVNDFVRGVSGGERKRVSIAEALAAKGSIYCWDNATRGLDASTAL
 EYAKAIRIMTNLLKSTAFVTIYQASENIYETFDKVTVLYSKGQIYFGLIHEAKPYFAKMGYLCPPTQAT
 AEFLTALTDPNGFLIKPGYENKPRTAEEFETYWLMSPEFAQMKKDIAAYKEVNTEKTKVEVYDESM
 QEKSXYTRKKSYYTWSYEQVKLCTQRGFQRIYGNKSYTVINVCSAIIQSFITGSLFYNTPSSTSGAFS
 RGGVLYFALLYSLMGLANIISFEHRPILQKHKGKSYLHPSAEEAGSTLASFPFRMIGLTCFIIILFFLS
 GLHRTAGSFTIYLFLTMCEAINGLFEMVSSVCDTLSQANSISGILMMSISMYSTYMIQLPSMHPWFK
 WISYVLPIRYAFESMLNAEFHGRHMDCANTLVPSSGDDYDNLSDDYKVCASFVGSKPGQSYVLGDDYLNQ
 FQYVYKHTWRNFGILWCFLLGYVVLKVIFTEYKRPVKGKDALIFKKGSKRFIAHADEESP DNVNDIDA
 KEQFSSSESSGANDEVFDDLEAKGFIWKCDCFTIIPYEGGKRMLLDNVSGYCIPGTMALMGESGAGKTT
 LLNTLAQRNVGIIITGDLVNGRPIDASFERRTGTVQOQODIHLIAELTVRESLQFSARMRRPQHLPDSEKM
 DYVEKIIIRVLMEEYAEALVGEVGCGLNVQERKQLS1GVELVAKEDLLLFLDEPTSGLDSQSSWAIQL
 LRKLSKAGQSIILCTIHQPSATLFEEDRLLLRLKGQQTVYFGDIGKNSATIINYFERNGARKCDSSENP
 AEYILEAIGAGATASVKEDWHEKWLNSVEFEQTKEVQDILNDSLQKETKSEVGDKPSKYATSYAYQFR
 YVLIRTSTSFWRSLNYSMSNMFHWSLVLITQYLSelpYHFFFSTIFFVSSYFPLRIFFEASRSAVYFLNYCIM
 FQLYYVGLMILYMPNLPSSANVILGLCLSFCGVTQPVSLMPGFWTFMWKASPYTYFVQNLVGI
 MLHKKPVVCKKKELNYFNPPNGSTCGEYMKPFLEKATGYIENPDATSDCAYCIYEVGDNYLTHISSKYS
 YLWRNFGIFWIYIFFNIIAMVCYVYLFHVRQSSFLSPVSLNKIKNIRKKKQ



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 00 87 0316
shall be considered, for the purposes of subsequent
proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
A	<p>DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; BIANCHET M A ET AL: "Modeling of nucleotide binding domains of ABC transporter proteins based on a F1-ATPase/recA topology: structural model of the nucleotide binding domains of the cystic fibrosis transmembrane conductance regulator (CFTR)" retrieved from STN Database accession no. 1998170885 XP002178151 & JOURNAL OF BIOENERGETICS AND BIOMEMBRANES, (1997 OCT) 29 (5) 503-24. , * abstract *</p> <p style="text-align: center;">—/—</p>	1-39
		CLASSIFICATION OF THE APPLICATION (Int.Cl.) C12N15/11 C07K14/705 A61K38/17 G01N33/68
		TECHNICAL FIELDS SEARCHED (Int.Cl.) C12N C07K A61K G01N
INCOMPLETE SEARCH		
<p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search: see sheet C</p>		
Place of search	Date of completion of the search	Examiner
THE HAGUE	25 September 2001	Masturzo, P
CATEGORY OF CITED DOCUMENTS		
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background D : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons B : member of the same patent family, corresponding document



European Patent
Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 00 87 0316

Although claims 1-9 (at least partially), 10-15, 23-25, 27, 29, 31, 33-34, 36-37 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Claim(s) not searched:
20, 22

Reason for the limitation of the search:

Claim 20, referring to a compound identified by the method of claims 1-9 and not further defined, could not be searched. Claim 22, referring to the applications of compounds of claim 20, was not searched as well.



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number

EP 00 87 0316

DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages		
A	N I TARASOVA ET AL.: "Inhibition of G-protein-coupled receptor function by disruption of transmembrane domain interaction" JOURNAL OF BIOLOGICAL CHEMISTRY. (MICROFILMS), vol. 274, no. 49, 3 December 1999 (1999-12-03), pages 34911-34915, XP002168073 AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD., US * the whole document *	1-39	
X	I N TARASOVA ET AL : "Disruption of transporter protein function by transmembrane domain analogs" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, SAN FRANCISCO, CALIFORNIA, USA, vol. 41, March 2000 (2000-03), page 398 XP001004628 * abstract *	1-39	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	WO 97 35881 A (GORDON NG ET AL.) 2 October 1997 (1997-10-02) * page 41 - page 44 *	1-39	
A	K-M COVITZ ET AL. : "Mutations that alter the transmembrane signalling pathway in an ATP binding cassette (ABC) transporter" EMBO JOURNAL., vol. 13, no. 7, 1994, pages 1752-1759, XP002178148 OXFORD UNIVERSITY PRESS, SURREY., GB ISSN: 0261-4189 * the whole document *	1-39	
		-/-	



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 87 0316

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	J A SHEPS ET AL.: "Hemolysin transport in Escherichia Coli" JOURNAL OF BIOLOGICAL CHEMISTRY. (MICROFILMS), vol. 270, no. 24, 16 June 1995 (1995-06-16), pages 14829-14834, XP002178149 AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD., US * the whole document *	1-39	
X	K-I KAWABATA ET AL.: "Protein interactions of Gtslp of Saccharomyces cerevisiae throughout a region similar to a cytoplasmic portion of some ATP-binding cassette transporters" EUROPEAN JOURNAL OF BIOCHEMISTRY, vol. 259, 1999, pages 112-119, XP002178150 BERLIN, DE ISSN: 0014-2956 * the whole document *	1-39	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
E	WO 01 36477 A (THE GOVERNMENT OF USA) 25 May 2001 (2001-05-25) * the whole document *	1-39	

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 00 87 0316

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

25-09-2001

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9735881	A	02-10-1997	AU CA WO EP	2020497 A 2250567 A1 9735881 A2 0906339 A2	17-10-1997 02-10-1997 02-10-1997 07-04-1999
WO 0136477	A	25-05-2001	AU WO	1922601 A 0136477 A2	30-05-2001 25-05-2001